Feverish illness in children: assessment and initial management in children younger than 5 years

Appendix H Evidence tables

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This guideline has been fully funded by NICE. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient.

Implementation of this guidance is the responsibility of local commissioners and/or providers

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Appendix H Evidence tables

2013 Evidence tables

Chapter 5

Review question

What is the value (as shown by likelihood ratios, sensitivity, specificity, positive predictive value and negative predictive value) of the following symptoms and signs, alone or in combination, as initial indications of serious illness?

- abnormal skin or mucosal colour (for example, pallor or cyanosis)
- appearing ill to a healthcare professional or parent/carer
- altered responsiveness or cry
- altered breathing (for example, nasal flaring, grunting, chest indrawing)
- abnormal respiratory rate, pulmonary (lung) crackles and other sounds
- oxygen desaturation
- dehydration
- prolonged capillary refill time, cold hands and feet
- poor feeding
- persistent fever (5 days or more)
- height of fever
- limb or joint swelling
- unwillingness to bear weight or use a limb
- bulging fontanelle
- rash (blanching or non-blanching)
- focal neurological signs

- focal seizures
- new lumps
- neck stiffness
- vomiting
- status epilepticus (prolonged or continuous fits).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Schwartz,S., Raveh,D., Toker,O., Segal,G., Godovitch,N., Schlesinger,Y., A week-by-week analysis of the low-risk criteria for serious bacterial infection in febrile neonates, Archives of Disease in Childhood, 94, 287-292, 2009 **Ref Id** 62778 **Country/ies where the study was carried out** Israel **Study type** Retrospective review **Aim of the study** To examine the reliability of 'low risk' criteria to exclude serious bacterial infection in febrile neonates (=< 28	**Sample size** n= 449 **Characteristics** Not reported Serious bacterial infection= 87 neonates (including bacteraemia; meningitis; UTI; combinations of bacteraemia, meningitis, and UTI; pneumonia; and omphalitis) **Inclusion criteria** All neonates presenting to the paediatric emergency room of a medical centre with a rectal temperature of => 38C measured in the ER or at home before arrival **Exclusion criteria** Birth before 37 weeks'	**Interventions**	**Details** Approval for this study was granted by the Human Rights Committee of Shaare Zedek Medical Centre. All neonates underwent the same sepsis evaluation: full blood count, blood culture, bladder catheterisation, or suprapbic aspiration for dipstick analysis and culture, lumbar puncture to obtain CSF for cell count., chemistry, culture, and when indicated, Gram stain. Chest radiograph was obtained when respiratory signs or symptoms were present. All infants were hospitalised and treated with intravenos antibiotics pending culture results. Authors were not blinded to culture results Criteria for being at low risk of SBI were (LRC+): not ill appearing, peripheral white blood cell count of 5000-15,000/mm^3, absence of leucocyte esterase in non-centrifuged urine on dipstick test, and <23 WBC/high power field on microscopic examination of the CSF. Infants who did not fulfil these four criteria were classified as LRC-. All infants were also classified with respect to the presence or absence of SBI. SBI was diagnosed (SBI+) if: a culture of blood, urine, CSF or stool grew a known bacterial pathogen, isolated growth of >1000 cfu/ml of a single skin bacteria, >1000 cfu/ml of at least one known	**Results** The mean (SD) ER temperature was slightly higher among those with SBI than those without (38.3 Cº (0.61) vs. 38.1 Cº (0.63), p=0.006). High fever as measured in the ER did not confer a statistically significant greater risk for SBI. Ill appearance: With SBI= 18 (33%) Without SBI= 37 (67%) Not ill appearance: With SBI= 69 (18%) Without SBI= 325 (82%) Ill appearance was significantly associated	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
days) according to age in weeks **Study dates** June 1997 to May 2006 **Source of funding** None reported	gestation Prior hospitalisation or receipt of antibiotics Known chronic disease Source of infection apparent on physical examination other than acute otitis media		urinary bacteria pathogen if two bacteria were isolated, and >10,000 cfu/ml of at least one known urinary pathogen if three organisms were isolated. The prevalence of SBI and the percentage of LRC+ cases which were SBI+ were calculated for each of the four weeks of life. T-test, chi square test (Fisher exact where applicable), and the linear trend analysis. 95% CI were calculated using the established mid-P method.	with SBI (p<0.001) SBI was diagnosed in 87 neonates Bacteraemia + meningitis + UTI= 2 Bacteraemia + meningitis = 1 Bacteraemia + UTI= 10 Bacteraemia= 1 UTI= 70 Pneumonia= 2 Omphalitis= 1	
Full citation Chen,C.J., Lo,Y.F., Huang,M.C., Chung,R.L., Tang,R.B., Wu,K.G., A model for predicting risk of serious bacterial infection in febrile infants younger than 3 months of age, Journal of the Chinese Medical Association: JCMA, 72, 521-526, 2009 **Ref Id** 83607 **Country/ies where the study was carried out**	**Sample size** n= 135 **Characteristics** < 29 days old= 60 => 29 days old= 75 Male= 90, female= 45 Ethnicity not reported **Inclusion criteria** < 3 months Admitted with fever -	**Interventions** Appearance	**Details** After admission, septic workup included a complete blood count, serum CRP analysis, urinalysis collected by urine bag, urine culture that was collected by suprapubic puncture or urinary catherisation, and blood cultures. Physical appearance was also graded by the attending paediatrician as either well or poor. Poor physical appearance was indicated by any of the following: decreased oral feeding, irritability, or any sign of dehydration (skin turgor, depressed fontanel, decreased urine output). If patients had diarrhoea, bedside stool smears were obtained and immediately examined for WBC count. Chest x-rays were performed and evaluated if respiratory symptoms were apparent. Lumbar puncture and cerebrospinal fluid analysis were performed if there was suspicion of central nervous system infection (i.e. seizure, irritability or drowsiness, bulging fontanel, toxic appearance with no infection focus). Each infant was treated with IV antibiotics while	**Results** Well appearance: With SBI= 22/34 No SBI= 83/101 Poor appearance: With SBI= 12/34 No SBI= 18/101 When comparing well appearance in SBI vs. no SBI and poor appearance in SBI vs. no SBI, p= 0.03	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Taiwan **Study type** Retrospective case series study **Aim of the study** To construct a model for predicting the risk of serious bacterial infection in febrile infants **Study dates** August 2003 to August 2004 **Source of funding** None reported	rectal temperature => 38C **Exclusion criteria** Premature (< 36 weeks) Underlying diseases (e.g. congenital heart disease, bronchopulmonary dysplasia, chronic lung disease, immunodeficiency, chromosome abnormalities, or congenital gastrointestinal tract anomalies). Hyperbilirubinemia or exhibiting an antenatal setup for sepsis (premature rupture of membranes, maternal fever, or peripartum antibiotics).		awaiting culture results. SBI included bacteraemia, bacterial meningitis, osteomyelitis, bacterial gastroenterocolitis, lobar pneumonia, and urinary tract infection. Differences between infants who did and did not have SBI were compared using Student's t-test or the Wilcoxon rank sum test for continuous data, and the X^2 or Fisher's exact test for categorical data. To determine the criteria for predicting SBI, 70% of the patients were randomly selected by simple random sampling for multivariate logistic regression. The estimated probabilities of having an SBI were obtained from the fitted model, and a cut-off point was selected for determining whether patients had SBI or not. The fitted regression model and the cut-off probability were then applied to the remainder of the patients for validation.		
Full citation Lacour,A.G., Gervaix,A., Zamora,S.A., Vadas,L., Lombard,P.R., Dayer,J.M., Suter,S., Procalcitonin, IL-6, IL-8, IL-1 receptor antagonist and C-reactive protein as identificators of serious bacterial infections in children with fever without localising signs, European Journal of Pediatrics, 160, 95-100,	**Sample size** n=124 **Characteristics** <u>Age:</u> 7 days to 36 months <u>Gender:</u> Not reported <u>Ethnicity:</u> Not reported	**Interventions** - Fever duration (h) - Temperature (C)	**Details** - Each infant was examined by a paediatric resident who took a complete history, performed a physical examination, recorded the degree and duration of fever and determined a clinical score according to McCarthy. - All children had a urine analysis and blood drawn for a white blood cell count and for determination of CRP, PCT, IL-6, IL-8 and IL-1Ra concentrations. - Children with leucocytes >15000/mm^3, band counts >1500/mm^3, leucocyturia or CRP >40mg/l had a blood culture, a urine culture, and a spinal tap when	**Results** <u>Fever duration</u> Benign infection (median and range): 24 hours (1-240) SBI: 27 hours (2-140) p value: 0.02 <u>Temperature</u>	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
2001 **Ref Id** 83852 **Country/ies where the study was carried out** Switzerland **Study type** Prospective observational study **Aim of the study** Whether the determination, in addition to the previously used parameters of PCT, IL-6, IL-8 or IL-1Ra offered an advantage in terms of sensitivity and specificity, with which a SBI could be predicted. **Study dates** March 1998-August 1999 **Source of funding** Not reported	**Inclusion criteria** - Children aged 7 days to 36 months - Rectal temperature >38C - Without localising signs of infection in their history or at physical examination **Exclusion criteria** - Children with fever lasting longer than 7 days - Neonates of less than 1 week - All children treated with antibiotics during the 2 previous days - Those with known immunodeficiencies (like neutropenia due to chemotherapy or HIV-infected children)		meningitis was suspected. They also received antibiotics for 48-72 hours until the results of the cultures were known. - All children had a clinical follow-up with physical examination by a paediatrician within the following 48 hours or by telephone. The diagnosis was registered at the end of the clinical follow up. - Infections requiring intravenous antibiotic therapy such as bacteraemia (positive blood culture), pyelonephritis (positive urine culture with $>10^4$ colonies/ml and a positive technetium 99M-dimercaptosuccinic acid (DMSA) renal scintigraphy at 4 days with a reversible cortical defect on the control scintigraphy at 90 days), lobar pneumonia (radiological diagnosis of lobar infiltrate by the radiologist in a blinded manner), meningitis (pleocytosis of >5cells/ul and a positive culture of CSF) or osteoarthritis were defined as SBI. - The remaining subjects suffered from infections classified as benign for the purpose of this study on the basis that they did not neither require oral antibiotic therapy at follow-up (probable viral infection) nor parenteral therapy for infections such as acute otitis media, lower UTI (negative renal DMSA scintigraphy), gastroenteritis or adenitis (focal infections). - Demographic characteristics and laboratory values of children with and without SBI were compared using the Fisher exact test for frequencies, the student t-test for normally distributed continuous variables and the Mann-Whitney U test otherwise. - The sensitivity, specificity, NPV and PPV for the detection of a SBI were determined for the McCarthy score and the different laboratory parameters. Binomial exact 95%CI were calculated for sensitivity and specificity.	Benign infection (mean and standard error): 39.0C +/-0.1 SBI: 39.1C +/-0.2 p value: NS SBI diagnosed in 28 children: Bacteraemia= 4 Pyelonephritis= 19 Lobar pulmonary condensation= 5	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			- The diagnostic accuracy of the different parameters and the best cut off points were determined with a ROC curve.		
Full citation Mandl,K.D., Stack,A.M., Fleisher,G.R., Incidence of bacteremia in infants and children with fever and petechiae, Journal of Pediatrics, 131, 398-404, 1997 **Ref Id** 83898 **Country/ies where the study was carried out** USA **Study type** Prospective and retrospective cohort study* **Aim of the study** To determine the incidence of serious invasive bacteremia caused by Neisseria meningitidis and other organisms in febrile infants and children with a petechial rash. Also, to study the diagnostic value of laboratory and clinical findings in these patients. **Study dates**	**Sample size** n= 411 **Characteristics** Age: </=18 years (57.7% of patients were between 3 and 36 months) Gender: Male (59.4%) Female (40.6%) Ethnicity: Not reported **Inclusion criteria** - </= 18 years - Temperature >/= 38C - A petechial rash **Exclusion criteria** - Patients with a history of malignancy, liver disease, acquired immunodeficiency syndrome or a chronic hematologic disorder	**Interventions** Ill appearance Purpura Petechiae	**Details** - A prospective cohort study in the emergency department of an urban paediatric teaching hospital was conducted during an 18-month period. Consecutive patients </=18 years with a temperature of 38C or higher and petechiae were enrolled. - Petechiae was defined as minute (<2mm in diameter), non-blanching, macular hemorrhagic spots in the skin, known to be new in onset by the health care providers, parents, or patient. - Subjects received routine care where most patients with fever and petechiae have a leukocyte count, blood culture, and if 18 months of age or older, a throat culture. - Subjects were categorized as appearing well and smiling, appearing well but not smiling, or crying but consolable. They were considered as appearing ill if they had a 'toxic' appearance, were irritable (inconsolably crying or screaming) or were lethargic. - Treating and attending physicians completed a brief questionnaire classifying the patient as appearing well or appearing ill, describing the number and location of petechiae and noting presence or absence of purpuric lesions. Any mechanical cause of the petechiae such as coughing, emesis, screaming, or compression from a tourniquet or blood pressure cuff was also assessed. Laboratory data was obtained through the hospital's computerized database. - To ensure inclusion of all eligible patients, the emergency department daily logs were inspected. Hospital admission logs were also searched for the diagnosis of 'fever and petchiae' or 'rule out	**Results** Ill appearance Serious invasive bacteremia= 6/6 No serious invasive bacteremia= 47/404 Sensitivity (95%CI): 1.00 (0.60, 1.00) Specificity (95%CI): 0.88 (0.86, 0.91) PPV (95%CI): 0.11 (0.01, 0.23) NPV (95%CI): 1.00 (0.97, 1.00) Purpura Sensitivity (95%CI): 0.83 (0.40, 0.99) Specificity (95%CI): 0.97 (0.95, 0.98) PPV (95%CI): 0.31 (0.05, 0.57) NPV (95%CI): 0.99 (0.99, 1.00) Petechiae 1: Serious invasive bacteremia= 0/6 No serious invasive bacteremia= 22/376 2 to 50: Serious invasive bacteremia= 3/6	**Limitations** *Hospital charts were reviewed to ensure eligible children were not missed, and therefore some children may have been enrolled retrospectively into the study (the authors do not report how many) Some febrile patients with viral syndromes may have had directed physical examinations and incomplete dermatologic inspection **Other information** - The authors note that petechiae are difficult to detect among darker

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
December 16, 1993 to June 30, 1995 **Source of funding** Not reported			meningococcemia'. If through this review, a patient not previously enrolled was identified, the attending emergency physician was immediately contacted to complete the questionnaire. - Investigators contacted patients by telephone 1 to 5 weeks after the visit. Health status of the child was obtained, as well as details of medical care provided during the interim weeks. At the end of the study period, the database of the hospital's bacteriology laboratory was searched for cases of meningococcemia potentially missed during enrolment. - For analysis, the following patients were grouped together: 1) those that had bacteremia or sepsis with invasive organisms 2) patients who had clinical sepsis with negative culture results. All these patients were considered to have serious invasive bacteremia. Those subjects with pneumococcal bacteremia and no evidence of sepsis were classified separately from those with serious invasive bacteremia.	No serious invasive bacteremia= 292/376 Too numerous to count: Serious invasive bacteremia= 3/6 No serious invasive bacteremia= 62/376 All children with serious invasive bacteremia had petechiae above and below the nipple line (6/6) <u>Purpura and petechiae</u> Serious invasive bacteremia= 5/6 No serious invasive bacteremia= 11/376 Bacterial illnesses: Bacteremia or clinical sepsis= 8 Neisseria meningitidis= 2 Clinical sepsis with negative blood culture result= 3 Group A streptococcus= 1 Streptococcus pneumoniae= 2 Positive CSF culture= 0/219 Throat positive for group A B-hemolytic streptococcus in those => 18 months= 40/154	skin patients - Laboratory test results were also reported in this study, but were not relevant to the review question
Full citation Pratt,A., Attia,M.W., Duration of fever and markers of serious bacterial infection in young febrile children, Pediatrics International, 49, 31-35, 2007 **Ref Id**	**Sample size** n= 119 **Characteristics** Median age: 10 months (range 1 to 34 months) Female: 55%	**Interventions** Duration of fever	**Details** The institutional review board at the DuPont Hospital approved the study protocol for children Data including age, gender, temperature at home and in the ED, duration of fever as reported by the caregiver and clinical observation using the Yale Observation Scale were collected prospectively and recorded on a standardised form. All patients had a CBC, blood culture, and CRP level drawn. A urinalysis and/or urine culture was obtained by bladder catheterisation on	**Results** Serious bacterial infections were based on laboratory or radiographic results (bacteraemia, meningitis, UTI, pneumonia, septic arthritis, and osteomyelitis). 17 patients had SBI, 102 did not <u>Fever =< 12 hours:</u> 45 patients	**Limitations** Convenience sample of patients **Other information** 7 patients were excluded due to an immediately

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
84029 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** To evaluate CRP as a predictor of SBI with respect to duration of fever. **Study dates** January 2002 to July 2003 **Source of funding** None reported	**Inclusion criteria** Children aged 1 to 36 months who presented with reported or documented fever => 39C No localising source of fever after careful history and physical exam by housestaff and attending paediatric emergency **Exclusion criteria** Those with an explainable cause of fever (e.g. acute otitis media, acute pharyngitis, acute respiratory tract infection, acute gastroenteritis) and those with a positive viral study were excluded. History of antibiotic use during the past 10 days, a known underlying immunologic disease, or vaccination during the previous 2 days.		patients under 6 months of age, as per current standards of care. A chest x-ray was performed at the discretion of the attending physician. Study subjects were divided into two groups based on duration of fever (=< 12 hours vs. > 12 hours). Patients in each time period and patients with and without SBI in each time period were compared using two-tailed t-test or Mann-Whitney U-test for variables expressed as means according to their parametric distribution. X^2 analysis was used to compare gender and SBI. Area under the curve statistics were used to compare bacterial markers in patients with SBI in both time periods. Sample size estimation was performed based on CRP as the most sensitive bacterial marker. On the hypothesis that the CRP mean value in patients with SBI in the =< 12 hour group will be 3mg/dl (+/- 2 mg/dL) and in the SBI patients in the >12 hour group will be 7 mg/dL (+/- 2 mg/dL), a minimum of six patients with SBI would need to be enrolled in each group to obtain a study power of 0.8	SBI= 6 (UTI= 5, bacteraemia= 1) SBI= 6/17 No SBI= 39/102 Median fever duration= 5 hours (range 1 to 12) Median temperature= 39.7C (range 39 to 40.9) Median YOS= 6 (range 6 to 15) <u>Fever > 12 hours:</u> 74 patients SBI= 11 (UTI= 8, pneumonia= 3) SBI= 11/17 No SBI= 63/102 Median fever duration= 36 hours (range 13 to 240) Median temperature= 40C (39 to 41.5) Median YOS= 6 (range 6 to 15)	identified source of fever or a positive viral rapid test 2 patients were excluded due to missing data regarding fever duration Occult bacteraemia= recovery of a single bacterial pathogen using standard culture techniques. UTI= growth of a single UTI pathogen at => 10^4 c.f.u./mL on a catheterized specimen Pneumonia= presence of a focal infiltrate on chest x-ray as interpreted by the paediatric radiologist
Full citation Rudinsky,S.L., Carstairs,K.L., Reardon,J.M., Simon,L.V., Riffenburgh,R.H., Tanen,D.A., Serious	**Sample size** n= 985 **Characteristics**	**Interventions** - Temperature >/=102.3F - Temperature	**Details** - Temperature measurements in the ED were rectal temperatures. SBI was defined as pneumonia, UTI, meningitis or bacteremia. - A specialised emergency treatment record was	**Results** Mean temperature: SBI= 103.3 +/- 1.2 No SBI= 103.2 +/- 1.2	**Limitations** Possible errors in data from incomplete medical records and reliance on

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
bacterial infections in febrile infants in the post-pneumococcal conjugate vaccine era, Academic Emergency Medicine, 16, 585-590, 2009 **Ref Id** 84072 **Country/ies where the study was carried out** USA **Study type** Cohort study with nested case-controls **Aim of the study** To identify the epidemiology of serious bacterial infections and the current utility of obtaining routine complete blood counts and blood cultures to stratify infants at risk of SBI, in the study population of febrile infants in the post-heptavalent pneumococcal conjugate vaccine (PCV7) era. **Study dates** December 2002-December 2003	Age: 0-24 months Gender: Male (55%) Female (45%) Ethnicity: Not reported **Inclusion criteria** - Children under 3 months of age and a home/ED temperature of >/=100.4F - Children between 3 and 24 months of age with a temperature >/=102.3F **Exclusion criteria** Not reported	>/=103F - Temperature >/=104F	developed and used for prospective data collection during this period. Age, sex, temperature (reported at home and in the ED) and final diagnosis were recorded. All parental reports of vaccination status were confirmed by reviewing a comprehensive electronic database into which every vaccine administered at the primary care clinics is entered. - A paediatric febrile pathway was in place in the ED. Infants less than 3 months were to have a CBC, blood culture, chest radiograph, lumbar puncture with cerebrospinal fluid analysis and culture, urinalysis, and urine culture obtained. Infants between 3 and 24 months were to have a CBC and blood culture. Chest radiographs, lumbar puncture, urinalysis and urine culture were performed if necessary. - Results of CSF studies, urinalysis, complete blood count, culture results, final radiology chest radiograph read, and immunization status were obtained from review of the electronic hospital archives. - Patient follow-up to determine any additional studies performed, admissions, or missed diagnoses during the study period was completed through review of the hospital electronic archives. Abstracted data were defined by the reviewers prior to the study. -UTI was defined as a positive urine culture, defined as >100,000 CFU of a single organism growth from a clean catch specimen, or >10,000 CFU in a catheter obtained specimen. Pneumonia was defined as a formal radiology read of the chest radiograph consistent with the presence of a lobar infiltrate. - Descriptive analysis was used for comparing two groups of febrile infants and children less than 24 months of age: those who were identified as having an SBI and those identified as not having an SBI. Fisher's exact test and chi-square analysis were used for binomial outcomes, with a p<0.05 taken for	P=0.26 Sensitivity, specificity, LR+ and LR- of temperature cut-offs for predicting SBI Temperature >/=102.3F Sensitivity (95%CI): 0.83 (0.75-0.88) Specificity (95%CI): 0.18 (0.16-0.21) LR+ (95%CI): 1.02 (0.93-1.11) LR- (95%CI): 0.93 (0.63-1.37) Temperature >/=103 Sensitivity (95%CI): 0.67 (0.59-0.75) Specificity (95%CI): 0.36 (0.33-0.39) LR+ (95%CI): 1.06 (0.93-1.20) LR- (95%CI): 0.90 (0.70-1.16) Temperature >/=104 Sensitivity (95%CI): 0.29 (0.22-0.38) Specificity (95%CI): 0.70 (0.67-0.73) LR+ (95%CI): 0.99 (0.75-1.32) LR- (95%CI): 1.00 (0.90-1.12)	electronic records Possible that the case definition of pneumonia, a formal radiology read of the chest X-ray consistent with the presence of a lobar infiltrate, may have overestimated the total number of pneumonia cases. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported			significance.		
Full citation Berger,R.M., Berger,M.Y., van Steensel-Moll,H.A., Dzoljic-Danilovic,G., rksen-Lubsen,G., A predictive model to estimate the risk of serious bacterial infections in febrile infants, European Journal of Pediatrics, 155, 468-473, 1996 **Ref Id** 85363 **Country/ies where the study was carried out** Netherlands **Study type** Prospective observational study **Aim of the study** To determine independent predictors of SBI in febrile infants using multivariate logistic regression analysis. **Study dates**	**Sample size** n=138 **Characteristics** Age: 2 weeks-1 year Gender: Male (56%) Female (44%) Ethnicity: Not reported **Inclusion criteria** - Infants aged 2 weeks-1 year - Rectal temperature >/=38C **Exclusion criteria** - Infants who were born preterm (gestational age <37 weeks), had perinatal complications, received antibiotics or had been vaccinated in the 48 hours preceding the visit, and infants with a known previous or underlying disease	**Interventions** - Duration of temperature >38C (hours) - Duration of temperature >48 hours - Diarrhoea - Temperature - Looking around the room - Moving arms and legs spontaneously - Reaching for objects - Colour (cyanotic or pale or flushed/mottled) - Clinical impression	**Details** - The study took place in the paediatric emergency ward of a hospital. The children are either self-referred or referred by a general practitioner. - Data on history, observation and physical examination were obtained using a standard form. - Clinical impression was standardised using a modification of variables proposed by McCarthy et al. - The child's looking around the room, spontaneous movement of arms and legs, reaching for objects, tonus and hydration were all scored on an ordinal scale (0=normal, 1=moderately impaired, 2=severely impaired). Skin colour was scored as normal or impaired. - The variables which appeared to be significantly associated with SBI in this population were then used to compose a 'standardised clinical impression score'. - Respiratory rates, signs of nuchal rigidity, of enteritis, of arthritis, a skin lesion or a positive urinalysis were considered as 'focal signs of infection'. - Laboratory data included WBC and differential counts, ESR, C-reactive protein and urinalysis. - All infants were re-evaluated 14 days after presentation. - The outcome variable was SBI, defined as bacterial growth in cultures from blood, CSF or urine or as growth of Salmonella, Shigella or Campylobacter	**Results** 33 had SBI, 105 did not Univariate analysis of clinical variables (RR and 95%CI) -Duration of temperature >38C 24 hours SBI= 15/33 No SBI= 65/105 48 hours SBI= 5/33 No SBI= 21/105 RR (compared to 24 hours)= 1.03 (95% CI 0.42 to 2.56) > 48 hours SBI= 13/33 No SBI= 19/105 RR (compared to 24 hours)= 2.17 (95% CI 1.17 to 4.03) -Diarrhoea SBI= 18/33 No SBI= 84/105 RR 2.35 (95% CI 1.34 to 4.18) -Temperature 38C SBI= 13/33 No SBI= 39/105 39C	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported **Source of funding** Not reported			species in stool. - Urinary tract infection was defined by a urine culture with >/=10^5 colonies/ml of a single organism. - Presumptive clinical diagnosis of otitis media, cellulitis, arthritis and osteomyelitis was regarded as SBI only in combination with bacterial growth in specimen culture from middle ear aspirate, soft tissue, joint and bone respectively. - Infants with a chest roentgenogram yielding pulmonary infiltrate, confirmed by an attending radiologist were considered as having serious illness and included in the SBI group. - Staphylococcus epidermis and other skin commensals were considered to be contaminants in this population of previous healthy infants. Those who defined the outcome were blinded for the predictive findings. - The results were compiled by a predesigned format, and subjected to univariate and multivariate analyses. The variables introduced in the logistic regression model were those with perceived clinical relevance, those identified by the univariate analysis or those reported as of diagnostic value by others.	SBI= 16/33 No SBI= 44/105 RR (compared to 38C)= 1.07 (95% CI 0.57 to 2.01) 40C SBI= 4/33 No SBI= 22/105 RR (compared to 38C)= 0.53 (95% CI 0.28 to 1.00) <u>Univariate analysis of variables used to standardize clinical impression</u> <u>-Looking around the room</u> Normal (score 0) SBI= 16/33 No SBI= 63/105 Moderately impaired (score 1) SBI= 7/33 No SBI= 32/105 RR (compared to normal)= 0.89 (95% CI 0.40 to 1.98) Severely impaired (score 2) SBI= 10/33 No SBI= 8/105 RR (compared to normal)= 2.74 (95% CI 0.82 to 5.00) (there are 2 infants from the no SBI group unaccounted for) <u>-Moving arms and legs spontaneously</u> Normal (score 0) SBI= 16/33	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				No SBI= 76/105 Moderately impaired (score 1) SBI= 9/33 No SBI= 23/105 RR (to normal) 1.34 (95% CI 0.66 to 2.72) Severely impaired (score 2) SBI= 8/33 No SBI= 4/105 RR (to normal) 3.83 (95% CI 2.11 to 6.98) <u>-Reaching for objects</u> Normal (score 0) SBI= 16/33 No SBI= 69/105 Moderately impaired (score 1) SBI= 5/33 No SBI= 24/105 RR (to normal) 0.92 (95% CI 0.37 to 2.28) Severely impaired (score 2) SBI= 10/33 No SBI= 10/105 RR (to normal) 2.66 (1.43 to 4.95) <u>-Colour(cyanotic or pale or flushed/mottled)</u> Normal SBI= 12/33 No SBI= 63/105 RR 2.08 (95% CI 1.12 to 3.89) <u>-Clinical impression</u> Normal (score 0 to 2) SBI= 12/33	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				No SBI= 71/105 Moderately ill (score 3 to 5) SBI= 8/33 No SBI= 22/105 RR (to normal) 1.84 (95% CI 0.84 to 4.07) Severely ill (score 6 to 8) SBI= 11/33 No SBI= 10/105 RR (to normal) 3.62 (95% CI 1.87 to 7.03) <u>Independent predictors of SBI selected in the logistic regression analysis</u> <u>-Duration of temperature >48h</u> Coefficient: 1.35 OR(95%CI): 3.85 (1.11-13.34) <u>-Clinical impression (0-8)</u> Coefficient: 0.20 OR(95%CI): 1.22 (0.95-1.57) <u>-A history of diarrhoea</u> Coefficient: 1.15 OR(95%CI): 3.15 (0.97-10.19) SBI was diagnosed in 33 infants: UTI= 9 (2 accompanied by bacteraemia) Meningitis= 6 (4 with bacteraemia)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Enteritis= 6 (no bacteraemia) Pneumonia= 5 (no bacteraemia) Arthritis/cellulitis= 2 (1 with bacteraemia) Purulent otitis media= 2 (no bacteraemia) Bacteraemia without focal signs of infection= 3	
Full citation Andreola,B., Bressan,S., Callegaro,S., Liverani,A., Plebani,M., Da,DaltL, Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department, Pediatric Infectious Disease Journal, 26, 672-677, 2007 **Ref Id** 93372 **Country/ies where the study was carried out** Italy **Study type** Prospective observational study **Aim of the study** To assess the value of procalcitonin and C-reactive protein compared with that of total white-blood cell count and	**Sample size** 408 children **Characteristics** Age: 10 months (2.5 to 16.5 months) Sex: 205 females 203 males **Inclusion criteria** Children younger than 3 years Fever of uncertain source Children who underwent blood analysis **Exclusion criteria** Antibiotic use in 48 hours prior to admission to	**Interventions** Fever duration Height of fever Yale score	**Details** Informed consent was obtained from the parents or legal guardians for the additional blood sampling. The study protocol was approved by the Hospital Ethics Committee. Complete history, demographic information, room temperature, degree and duration of fever, physical examination, and YOS were recorded at the time of initial evaluation. Admission to the hospital was mandatory for all neonates. For older infants and children, decisions on therapy and hospitalisation were made by the attendant physician. Follow-up of all non-hospitalised patients was performed by telephone contact or clinical assessment by a paediatrician within the next 72 hours. The final diagnosis was registered at the end of the follow up. On the basis of their final diagnosis, children were classified into two groups: patients with (SBI group) or without (non-SBI group) serious bacterial infections. The following were considered as SBI: bacteraemia (recovery of a single bacterial pathogen using standard culture techniques), acute pyelonephritis (growth of a single urinary tract pathogen at $\geq 10^5$ colony-forming units/mL in 2 consecutive urine samples and presence of a renal hypocaptation at DMSA scan performed within the first week after admission), lobar pneumonia (presence of focal infiltrate on chest radiograph observed by the paediatric radiologist in a blinded manner), bacterial meningitis (positive cerebrospinal	**Results** SBI= 94 (23%) children Non-SBI= 314 (77%) children Fever duration <8 hours: SBI= 14/94 Non-SBI= 31/314 Fever duration 8 to 24 hours: SBI= 31/94 Non-SBI= 67/314 Fever duration > 24 hours: SBI= 49/94 Non-SBI= 216/314 (no significant different between groups for fever duration) Max temperature: SBI= 39.2 +/- 0.8 Non-SBI= 39.0 +/- 0.8 (p= 0.004) Yale score <10: SBI= 46/94 Non-SBI= 225/314 Yale score 10 to 16: SBI= 40/94	**Limitations** Not all children over three months had blood culture performed **Other information** Of a total of 435 children that presented, 16 were not enrolled 'for inadvertent omission', and 11 children were excluded for a lack of follow up

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
absolute neutrophil count, in predicting severe bacterial infections in febrile children admitted to an Emergency Department. **Study dates** May 2004 to October 2005 **Source of funding** None reported	hospital Vaccination in previous 2 days Known immunodeficiencies Chronic pathology Fever lasting longer than 5 days		fluid culture), bone or joint infections (local isolation or isolation in blood culture of a microorganism), and sepsis (defined according to Levy et al. - signs and symptoms of inflammation plus infection, tachycardia, decreased capillary refill or mottling, and at least one of the following indications of altered organ function as altered mental status, hypoxemia, increased serum lactate level, or bounding pulses, coagulation abnormalities.). Remaining children with negative cultures or clinical improvement without antibiotic therapy or with detection of a focal infection at follow-up were classified in the non-SBI group.	Non-SBI= 82/314 Yale score > 10: Sensitivity= 38.3 Specificity= 67.8 LR+ 1.19 LR- 0.91 Yale score > 16: SBI= 8/94 Non-SBI= 7/314 (P= 0.0001) 217 (53%) children were hospitalised SBIs: Escherichia coli= 53 Pseudomonas aeruginosa= 2 Enterococcus faecalis= 1 Klebsiella pneumoniae= 1 Proteus mirabilis= 1 Streptococcus pneumoniae= 7 Streptococcus Group B= 9 Staphylococcus aureus= 4 Non-SBIs: Focal bacterial infection= 64 (16%) (24 lower UTIs, 23 pharingotonsillitis, 7 otitis, 3 adenitis, 3 cellulitis, 2 gastroenteritis, 2 scarlet fever) Proved viral infection= 36 (9%) (positive antigen detection or viral culture, characteristic evolution of disease) Probable viral infection= 213 (52%) (negative cultures, spontaneous recovery without antibiotics and no signs for focal bacterial infection at clinical follow up).	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				1 case of Kawasaki disease (classed as non-SBI)	
Full citation Galetto-Lacour,A., Zamora,S.A., Gervaix,A., Bedside procalcitonin and C-reactive protein tests in children with fever without localizing signs of infection seen in a referral center, Pediatrics, 112, 1054-1060, 2003 **Ref Id** 93988 **Country/ies where the study was carried out** Switzerland **Study type** Prospective observational study **Aim of the study** To assess the value of bedside tests for predicting the occurrence of severe bacterial infections (SBIs) in children with fever without source. **Study dates**	**Sample size** n=110 **Characteristics** Age: 7 days to 36 months Gender: Not reported Ethnicity: Not reported **Inclusion criteria** - Children aged 7 days to 36 months - Rectal temperature >/=38C - No localizing signs of infection in their history or at physical examination **Exclusion criteria** - Children with fever lasting longer than 7 days - Children who were	**Interventions** - YOS score >10 - Fever duration (h) - Fever (C)	**Details** - Children were examined by a paediatric resident who took a complete history, performed a physical examination, recorded the degree and duration of fever, and determined a clinical score, according to McCarthy - All children had a WBC count with differential and a determination of CRP, PCT, and IL-6 values - Decisions on antibiotic treatment and hospitalization were made by the resident in charge of the patient, based on clinical assessment and the presence of biological risk factors. - All children had a clinical follow-up with physical examination by a paediatrician in the following 48 hours or by telephone contact. Antibiotics were discontinued after 48-72 hours if the results of the cultures were negative. The diagnosis was registered at the end of the clinical follow-up. - Definition and criteria of SBI's were 1) bacteremia, positive blood culture 2) pyelonephritis, positive urine culture with $>10^5$cfu/mL and cortical defect seen at the DMSA renal scintigraphy 3) lobar pneumonia, lobar consolidation diagnosed on a chest radiograph by a paediatric radiologist unaware of the study 4) bacterial meningitis, CSF pleocytosis of >5cells/uL and positive culture of CSF 5) deep abscess, assessed by computed tomography scan and surgical exploration. - Children were classified as having a benign infection for the purpose of this study on the basis of 1) negativity of blood or CSF culture 2) positive urine culture with a normal DMSA renal scintigraphy 3) clinical improvement without antibiotics 4) the presence	**Results** YOS score >10 Sensitivity, % (95%CI): 23 (5-54) Specificity, % (95%CI): 82 (67-92) PPV (%): 76 NPV (%): 30 Fever duration (h) Benign infection (median [range]): 24 (1-140) SBI (median [range]): 48 (6-140) P value: 0.026 Fever (C) Benign infection (median [range]): 39.5 (38-40.8) SBI (median [range]): 39.4 (38.3-41) P value: NS	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported **Source of funding** Not reported	treated with antibiotics during the 2 previous days - Those with known immunodeficiencies		of a focal infection at the follow-up visit such as otitis media or gastroenteritis. - Demographic characteristics and laboratory values of children with benign infection and SBI were compared using the Fisher exact test for frequencies, the t test for normally distributed continuous variables and the Mann-Whitney U test otherwise. - The sensitivity, specificity, NPV and PPV for the detection of an SBI were determined for the McCarthy score and the different laboratory parameters.		
Full citation Nademi,Z., Clark,J., Richards,C.G., Walshaw,D., Cant,A.J., The causes of fever in children attending hospital in the north of England, Journal of Infection, 43, 221-225, 2001 **Ref Id** 94746 **Country/ies where the study was carried out** UK **Study type** Non-interventional observational prospective study **Aim of the study** To assess the causes of	**Sample size** n=141 **Characteristics** Age: 8 days to 16 years (mean: 3.3 years) Gender: Male (64%) Female (36%) Ethnicity: Not reported **Inclusion criteria** - All patients presenting with fever to the paediatric assessment units at Newcastle General Hospital and Royal Victoria Infirmary in Newcastle between 1 August and 31 October 1999	**Interventions** Temperature >39C Temperature >39.5C Poor feeding Vomiting Restlessness Petechial rash	**Details** - Subjects were all patients presenting with fever to the paediatric assessment units at Newcastle General Hospital and Royal Victoria Infirmary in Newcastle between 1 August and 31 October 1999 - Axillary temperature was measured routinely in children under 3 years of age; tympanic temperature in children older than 3 years of age. Fever was defined as temperature >/= 38 degrees. - Registrars and Senior House Officers were asked to record details of the history, examination, laboratory tests and management on a structured questionnaire based on acute illness observation scales designed to record the signs and symptoms of infection and laboratory results obtained. - These were checked against the case notes and nursing records and grouped with the aid of specific definitions and clinical diagnosis. - Clinical management was the responsibility of the duty paediatric team who decided on the need for investigations such as lumbar puncture, whether to admit the child or whether to give IV antibiotics.	**Results** Temperature >39C with 95%CI Raw data not reported Sensitivity(%): 14 (3-25) Specificity(%): 82 (74-89) PPV(%): 25 (7-42) NPV(%): 70 (61-78) Temperature >39.5C with 95%CI Raw data not reported Sensitivity(%): 7 (0-15) Specificity(%): 93 (87-98) PPV(%): 30 (1-58)	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
fever and identify clinical and laboratory features suggesting serious disease in UK children presenting to hospital with temperatures >/= 38C **Study dates** Not reported however patients presented with fever between 1 August and 31 October 1999 **Source of funding** Not reported	**Exclusion criteria** - Patients with a temperature less than 38C		- Patients who appeared toxic or had signs and symptoms of serious infection or had a high WBC count (>15000/mm^3) without an apparent focus of bacterial infection such as otitis media or pneumonia were admitted or kept for a while for observation. - Children less than 24 months and temperature > 39.5C and WBC>/=15000/mm^3 were also admitted for further investigation. Most medical staff advocated a full septic screen for febrile children less than 3 months of age.	NPV(%): 71 (63-78) <u>Poor feeding with 95%CI</u> Serious disease= 32/41 No serious disease= 57/100 Sensitivity(%): 78 (65-90) Specificity(%): 43 (33-52) PPV(%): 36 (25-45) NPV(%): 83 (72-92) Present in 32/41 (78%) of children with serious diseases and in 57/100 (57%) of children with non-serious diseases <u>Vomiting with 95%CI</u> Raw data not reported Sensitivity(%): 59 (43-73) Specificity(%): 60 (50-69) PPV(%): 38 (25-49) NPV(%): 78 (68-87) <u>Restlessness with 95%CI</u> Serious illness= 31/41 No serious illness= 57/100	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Sensitivity(%): 76 (62-88) Specificity(%): 43 (33-52) PPV(%): 35 (25-45) NPV(%): 81 (70-91) Present in 31/41 (76%) of children with serious diseases and in 57/100 (57%) of children with non-serious diseases Petechial rash with 95%CI Serious illness= 11/41 No serious illness= 3/100 Sensitivity(%): 29 (15-43) Specificity(%): 98 (95-100) PPV(%): 86 (67-100) NPV(%): 77 (69-84) Present in 11/41 (27%) of children with serious diseases and 3/100 (3%) of children with non-serious diseases	
Full citation Shin,S.H., Choi,C.W., Lee,J.A., Kim,E.K., Choi,E.H., Kim,H.S., Kim,B.I., Choi,J.H., Risk factors for serious bacterial infection in febrile young infants in a community referral hospital, Journal of Korean Medical Science,	**Sample size** 221 children **Characteristics** Mean age at visit= 43 +/- 25 days old (34% ≤ 30 days old, 39% 31 to 60 days old, 27% 61 to 90	**Interventions** Non-bacterial infection= 170 Serious bacterial infection= 41	**Details** The institutional review board approved the study. Parents gave informed consent for their children to be included in the study. All infants underwent a complete sepsis workup, the indication of which was an ill-looking appearance or a fever of => 39C. Body temperature was measured at the axilla, and the highest body temperature during the	**Results** Peak of fever: With SBI= 38.7C (+/- 0.5) Without SBI= 38.6 (+/- 0.4) p= 0.34 Lethargy: With SBI= 7 (17%) Without SBI= 48 (28%)	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
24, 844-848, 2009 **Ref Id** 95263 **Country/ies where the study was carried out** South Korea **Study type** Prospective observational study **Aim of the study** To develop clinical criteria to help guide clinicians in distinguishing high-risk vs. low risk febrile infants for serious bacterial infection among infants younger than three months old in a community referral hospital. **Study dates** August 2003 to July 2006 **Source of funding** None reported	days old). "Male infants were 1.7 fold more common than female infants" **Inclusion criteria** < 3 months old ≥ 38C axillary temperature Fever of unknown focus Children who were directly hospitalised on suspicion of neonatal sepsis **Exclusion criteria** Evident comorbid condition such as pneumonia, bronchiolitis, gastroenteritis, and arthritis Preterm infants who had fever in the neonatal intensive care unit Term infants who had fever within the first 72 hours after birth		stay in the ED or outpatient clinic was recorded. Complete sepsis workup included blood and urine cultures, complete blood cell count, CRP, urinalysis with microscopic examination of urinary sediment, chest radiography and lumbar puncture. CSF samples from lumbar punctures were used for cell counts, chemistry including glucose and protein, bacterial and fungal cultures, viral cultures and PCR. Febrile illness without a documented cause (FISDC) was applied when the fever subsided spontaneously within five days after admission and the febrile infant left hospital without any complications or sequelae Aseptic meningitis - CSF pleocytosis with a negative CSF culture Bacterial meningitis - CSF pleocytosis with a positive CSF culture Bacteraemia - positive blood culture with or without sepsis syndrome UTI - culture-positive (≥ 10^5 CFU/HPF) urine obtained by a urine bag with a concurrent marked pyuria (WBC ≥ 50/HPF)	p= 0.14 Irritability: With SBI= 14 (34%) Without SBI= 63 (37%) p= 0.78 Poor feeding: With SBI= 11 (27%) Without SBI= 63 (37%) p= 0.24 Ill-looking appearance: With SBI= 15 (37%) Without SBI= 53 (31%) p= 0.46 Moaning sound: With SBI= 8 (20%) Without SBI= 20 (12%) p= 0.19 Mild URI symptoms: With SBI= 2 (5%) Without SBI= 48 (28%) p < 0.01 Mild GI symptoms: With SBI= 6 (15%) Without SBI= 19 (11%) p= 0.54 Febrile illness without a documented cause= 142 (63%) Aseptic meningitis and/or isolated UTI= 28 (13%) Isolated bacteraemia= 6 (3%) Bacterial meningitis= 4 (2%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				UTI with concurrent bacteraemia= 3 (1%) Rotaviral gastroenteritis= 1 Kawasaki disease= 2 Pneumonia= 2 Acute otitis media= 1 Influenza virus infection= 1 Respiratory syncytial virus bronchiolitis= 1 "Miscellaneous"= 2 (of the 13 with bacteraemia, 7 were caused by group B Streptococcus, 3 by Escherichia coli, 1 each of Streptococcus pneumoniae, Staphylococcus aureus, and Streptococcus pyogenes. All cases of bacterial meningitis were caused by group B Streptococcus)	
Full citation Weber,M.W., Carlin,J.B., Gatchalian,S., Lehmann,D., Muhe,L., Mulholland,E.K., WHO Young Infants Study Group., Predictors of neonatal sepsis in developing countries, Pediatric Infectious Disease Journal, 22, 711-717, 2003 **Ref Id** 95588 **Country/ies where the study was carried out** Ethiopia, The Gambia, Papua New Guinea and The Philippines **Study type** Prospective observational	**Sample size** n= 3303 **Characteristics** <u>Age:</u> 0-59 days <u>Gender:</u> Not reported <u>Ethnicity:</u> Not reported **Inclusion criteria** - Infants <2 months of age presenting with illness to health facilities in Ethiopia, The Gambia, Papua New Guinea and The Philippines **Exclusion criteria**	**Interventions** - History of cough - History of fast breathing - History of change in level of activity - History of change in crying - History of convulsion - History of feeding problem - Lower chest wall indrawing	**Details** - The study was conducted at hospitals or outpatient clinics (in Ethiopia, The Gambia, Papua New Guinea and The Philippines) where large numbers of sick infants are seen. - All infants underwent a standardized history and physical examination to assess the presence or absence and the degree of severity of signs and symptoms believed to be associated with bacterial disease. Infants with pre-specified symptoms associated with possible bacterial infection underwent a laboratory evaluation. - Study outcome measures were defined as follows: 1) Sepsis: the growth of a known pathogen in cultures of blood 2) Meningitis: a positive cerebrospinal fluid culture 3) Hypoxemia: an adjusted oxygen saturation below 90% (severe hypoxemia) or between 90% and below	**Results** <u>Association of clinical signs with sepsis</u> - Temperature <35.5C OR: 3.7 95%CI: (1.8, 7.3) - Temperature >/=38C OR: 3.6 95%CI: (2.6, 5.1) <u>Association of clinical signs with meningitis</u> - Temperature <35.5C OR: 4.2 95%CI: (0.8, 22.5) - Temperature >/=38C OR: 11.8 95%CI: (5.7, 24.6)	**Limitations** Whereas the 3 sites, The Philippines, Ethiopia and The Gambia were not significantly different, signs generally performed more poorly in Papua New Guinea. The sensitivity was generally lower and the specificity higher in Papua New Guinea, indicating a shift in the receiver operating characteristic curve to the left. This indicates

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study **Aim of the study** To identify the value of individual signs and of a range of very simple combination rules that would be suitable for use in a wide range of primary care settings in different countries **Study dates** Not reported **Source of funding** Study was supported by the United States Agency for International Development and the WHO Program for the Control of Acute Respiratory Infections	- Children with a diagnosis of congenital heart disease and hypoxemia	- Nasal flaring - Grunting - Crepitations - Wheeze or rhonchi - Conscious state drowsy/unconscious - Conscious state agitated - Arousal state lethargic/unconscious - Feeding ability reduced - No spontaneous movement - Consolability: continues to cry/fuss - Central cyanosis - Dehydration - Digital capillary refill 2+ s - Umbilical	95% (mild hypoxemia) - An ordinal scale that summarized the presence or absence of disease as well as its severity was developed and used for primary analysis because it allowed infants who might have negative cultures (e.g.: those with low oxygen saturation and positive chest radiographs) to be classified as severely ill, because they might well be at increased risk of bacterial infection. - Diagnoses were ranked in a hierarchical fashion based on their association with the most severe outcome, death. Diagnoses not strongly related to death were examined with respect to their association with the presence of a positive blood culture or CSF result. - Historical factors and clinical signs predicting sepsis, meningitis, hypoxemia, deaths and an ordinal scale indicating severe disease were investigated by logistic regression and the performance of simple combination rules was explored.	<u>Association of clinical signs with death</u> - Temperature <35.5C OR: 3.1 95%CI: (1.8, 5.3) - Temperature >/=38C OR: 2.3 95%CI: (1.7, 3.2)	that some caution should be exercised in extrapolating findings from one site to others. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		discharge - Bulging fontanel - Respiratory rate <40 - Respiratory rate >/= 60 - Temperature <35.5C - Temperature >/=38C - Hypoxemia - Invasive bacterial infection - Meningitis			
Full citation Wells,L.C., Smith,J.C., Weston,V.C., Collier,J., Rutter,N., The child with a non-blanching rash: how likely is meningococcal disease?, Archives of Disease in Childhood, 85, 218-222, 2001 **Ref Id** 95592 **Country/ies where the study was carried out**	**Sample size** n=218 **Characteristics** Age: </=15 years Gender: Not reported Ethnicity: Not reported	**Interventions** - Fever >38.5C - Fever >37.5C - Fever 37.5-38.5C	**Details** - A member of the paediatric medical team collected data in the children's accident and emergency department, entering it on a standard proforma at the time of presentation of the child. - The following data were recorded: presenting signs and symptoms including axillary temperature, blood pressure (hypotension defined as 2 SD or more below the mean for age), capillary refill time (normal if less than 2 secs) and details of the rash (size and distribution). Children were also characterised as being either well (smiling or crying but consolable) or ill (toxic, irritable and crying inconsolably, or lethargic). - The following investigations were sent: full blood	**Results** Fever >38.5C Non-meningitis group= 37/194 Meningitis group= 14/24 OR 8.0 (2.7 to 23.8) Sensitivity, 95% CI (%): 58 (39-78) Specificity, 95% CI (%): 81 (75-86) PPV, 95% CI (%): 27 (15-40) NPV, 95% CI (%): 94 (88-100) Fever 37.5 to 38.5C Non-meningitis group= 51/194 Meningitis group= 5/24	**Limitations** Study authors admit that some children with a rash but no meningococcal disease may have been sent home without being enrolled in the study Data collection was performed by different

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
UK **Study type** Prospective observational study **Aim of the study** To determine whether it is possible to predict which children with a non-blanching rash do or do not have meningococcal infection, based on the characteristics of the rash, other physical signs, and simple laboratory investigations at the time of presentation. **Study dates** 1 November 1998-31 October 1999 **Source of funding** Not reported	**Inclusion criteria** - Children aged 15 years or less with a non-blanching rash who presented to the children's accident and emergency department between 1 November 1998 to 31 October 1999. **Exclusion criteria** - Children who had a clear alternative diagnosis (e.g.: Henoch-Schonlein purpura, idiopathic thrombocytopenic purpura, haemolytic uraemic syndrome, acute leukaemia, clotting disorder).		count, differential white cell count, clotting studies, C reactive protein, blood culture, and polymerase chain reaction for meningococcal DNA. CSF was sent for microscopy, bacterial and viral culture, PCR, glucose and protein when a lumbar puncture was clinically indicated. - Proformas were completed at the time for 197 patients; 21 (9.8%) were completed retrospectively from the case notes after patients were identified by cross checking during or at the end of the study period. - Meningococcal infection was defined using the PHLS Communicable Disease Surveillance Centre enhanced surveillance for meningococcal disease definition of a positive blood, CSF or skin culture for Neisseria meningitidis, Gram negative diplococci in CSF, or positive PCR for meningococcal DNA from blood or CSF. - Children who had proven meningococcal disease were compared with those who did not using univariate analysis. Numbers were too small for multivariate analysis. Odds ratios and 95%CIs were calculated. - Specificity, sensitivity, PPV and NPV for a range of variables were also calculated.	OR 2.1 (0.58 to 7.5) <u>Fever >37.5C</u> Non-meningitis group= 88/194 Meningitis group= 19/24 Sensitivity, 95% CI (%): 79 (63-95) Specificity, 95% CI (%): 55 (48-62) PPV, 95% CI (%): 18 (11-25) NPV, 95% CI (%): 95 (88-100)	grades of doctor **Other information**
Full citation Yeboah-Antwi,K., ddo-Yobo,E., du-Sarkodie,Y., Carlin,J.B., Plange-Rhule,G., Osei,Akoto A., Weber,M.W., Hamer,D.H., Clinico-epidemiological profile and predictors of severe illness in young infants (0-59 days) in	**Sample size** n=685 **Characteristics** <u>Age:</u> 0-59 days <u>Gender:</u> Not reported	**Interventions** Temperature >/=37.5C	**Details** - A staff nurse (study person A) evaluated each infant using a structured form. The infant was then referred to a paediatrician experienced in neonatal care (study person B) who was blinded to study person A's findings, for comprehensive clinical evaluation which included history, examination and the arranging of any clinically indicated laboratory investigations. - Pulse oximetry was performed on all patients and	**Results** <u>OR for temperature>/= 37.5C for predicting serious illness</u> <u>Age 0-6 days</u> OR: 7.4	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ghana, Annals of Tropical Paediatrics, 28, 35-43, 2008 **Ref Id** 95643 **Country/ies where the study was carried out** Ghana **Study type** Prospective study **Aim of the study** To describe the clinical profile of sick young infants presenting to a hospital and to define important signs and symptoms that will enable health workers to detect young infants with severe illness requiring hospital admission. **Study dates** September 2002-September 2003 **Source of funding** Financial support through a co-operative agreement between Boston University and the Office of Health and Nutrition of the United	Ethnicity: Not reported **Inclusion criteria** -Infants <2 months **Exclusion criteria** -Infants requiring immediate cardiopulmonary resuscitation, hospitalised in the previous 2 weeks (except for delivery), referred from another health care facility, having an obvious lethal congenital abnormality, residing 15km or more away from the hospital or having previously participated in the study.		clinical findings were documented. Within 2 hours of the infant's initial assessment study person B determined whether the infant had any serious disease that required admission or could be sent home with appropriate treatment, if necessary. Study person B's assessment was the gold standard for the primary outcome. - Admitted patients were managed according to standard hospital procedures and the infant's clinical progress was followed. The final diagnosis and outcome of hospitalisation were documented on form C. - Various laboratory tests as required were performed. - All patients who were sent home were advised to return for re-evaluation within 48-72 hours. At follow-up, it was decided whether the child was well or sick and needed hospitalisation. If they did not return for follow-up within 24 hours of the scheduled appointment, a study team member made a home visit within 7 days of the initial hospital visit. - Analysis included univariate analysis of the association between 'severe illness requiring hospital admission' and individual clinical signs and symptoms, tabulation of sensitivity and specificity, and estimation of odds ratios with 95%CI's.	95%CI: 3.0-18.5 Age 7-27 days OR: 11.1 95%CI: 5.2-24.1 Age 28-59 days OR: 7.4 95%CI: 2.8-19.5	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
States Agency for International Development.					
Full citation Bang,A., Chaturvedi,P., Yale Observation Scale for prediction of bacteremia in febrile children, Indian Journal of Pediatrics, 76, 599-604, 2009 **Ref Id** 118632 **Country/ies where the study was carried out** India **Study type** Diagnostic accuracy study **Aim of the study** To assess the accuracy and reliability of Yale observation scale (YOS) predicting bacteremia **Study dates** Not reported (study published in 2009) **Source of funding** None reported	**Sample size** n=219 **Characteristics** Age: Mean= 15.24 months, Range 3 to 36 months Gender: Male 60%, Female 40% Ethnicity: Not reported **Inclusion criteria** Children aged 3 to 36 months who were admitted to the paediatric ward of Mahatma Gandhi Institute of Medical Sciences (MGIMS) Documented fever (rectal temperature >38C) **Exclusion criteria** - Children who developed fever more than 8 hours after they were admitted to the hospital - Children who were known to have an	**Interventions** Yale observation scale - Quality of cry Normal: strong with normal tone or content and not crying Moderate impairment: whimpering or sobbing Severe impairment: weak or moaning or high pitched - Reaction to parent stimulation Normal: Cries briefly then stops or content and not crying Moderate impairment: cries off and on Severe impairment: continual cry or hardly response - State variation Normal: If awake, stays awake or if asleep and stimulated, wakes up quickly Moderate impairment: eyes	**Details** - 219 consecutive febrile inpatients aged 3-36 months were the subjects - Before giving antipyretics, rectal temperature was recorded - YOS scores were assessed by 2 independent blinded residents - History, clinical examination and investigations followed - Blood cultures were taken in all children before antibiotics - Point estimates and 95%CIs were calculated for sensitivity, specificity, positive and negative predictive values and likelihood ratios for use of YOS as a diagnostic test in prediction of bacteremia - The best cut off value for a positive YOS test was established by calculating these statistical values separately for a cut off YOS score of 8, 10 and 12 and plotting ROC curve. -Reliability of YOS was assessed by the inter-observer agreement through kappa statistics	**Results** Diagnostic value of various YOS scores for prediction of bacteremia YOS score >8 True positives=56 False positives=51 True negatives=97 False negatives=2 Total=206 Sensitivity=96.55(79.3,98.6) Specificity=65.54(55.2,71.6) PPV=52.34(42.5,62.1) NPV=97.98(92.9,99.8) +LR=2.80(2.23,3.52) -LR=0.05(0.01,0.21) YOS score >10 True positives=51 False positives=24	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	immunodeficiency state	close briefly awakes with prolonged stimulation Severe impairment: awake or falls to sleep or does not wake up - Colour Normal: pink Moderate impairment: pale extremities or acryocyanosis Severe impairment: pale or cyanotic or mottled ashen - Hydration Normal: skin normal, eyes normal and mucous membranes moist Moderate impairment: skin, eyes - normal AND mouth slightly dry Severe impairment: skin doughy/tented and dry mucous membrane and/or sunken eyes - Response (talk, smile) to social overtures Normal: smiles or alerts (=/< 2 months) Moderate impairment: brief smile or alerts		True negatives=124 False negatives=7 Total=206 Sensitivity=87.93(71.0,92.8) Specificity=83.78(73.0,87.3) PPV=68.0(56.2,78.3) NPV=94.66(89.3,97.8) +LR=5.42(3.71,7.92) -LR=0.14(0.07,0.29) YOS score >12 True positives=28 False positives=13 True negatives=135 False negatives=30 Total=206 Sensitivity=48.28(26.9,56.0) Specificity=91.22(67.3,89.8) PPV=68.29(51.9,81.9)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		briefly (=/< 2 months) Severe impairment: no smile, face anxious/dull/expressionless or no alerting (=/< 2 months)		NPV=81.82(75.1,87.4) +LR=5.5(3.0,9.8) -LR=0.57(0.44,0.73)	
Full citation Hsiao,A.L., Chen,L., Baker,M.D., Incidence and predictors of serious bacterial infections among 57- to 180-day-old infants, Pediatrics, 117, 1695-1701, 2006 **Ref Id** 118663 **Country/ies where the study was carried out** USA **Study type** Prospective study **Aim of the study** To investigate the etiology of fever and usefulness of screening tests in older (2-6 months) infants. **Study dates** February 2003-February	**Sample size** n=429 **Characteristics** Age: 57-180 days (2-6 months) Gender: Male (51%) Female (49%) Ethnicity: Not reported **Inclusion criteria** - 57-180 days old (2-6 months) - Rectal temperature > 37.9C **Exclusion criteria**	**Interventions** - Yale Observation Scale - Duration of fever - Temperature/height of fever	**Details** - Infants 57-180 days of age with rectal temperatures >37.9C who consecutively presented to the emergency department of Yale-New Haven Children's Hospital were prospectively enrolled after informed consent. - All children underwent a complete evaluation including history and physical examination and scoring of clinical appearance using the Yale Observation Scale (YOS). - A standard laboratory examination was also carried out. Additional studies such as chest radiograph, lumbar puncture, and stool studies, were performed at the discretion of the attending physician. - Clinicians were asked to note the presence or absence of an obvious source of fever after physical evaluation of the patient and before return of laboratory or other studies. - Informed signed consent was obtained from the guardians of infants. Age, gender, laboratory results, historical details and physical examination findings were recorded. - Bacterial culture results were monitored until their completion, typically 2 days for urine cultures and 5 days for blood and cerebrospinal fluid cultures. Urine cultures were considered positive if there were >10000 colonies of a single organism per mL. Positive culture results were reported to the paediatric emergency department physician staff and primary care	**Results** Summary of potential predictors of SBI (mean +/- SD) YOS Infants with SBI: 9.4 +/- 4.6 Infants without SBI: 8.1 +/- 3.6 P<0.05 Duration of fever, h Infants with SBI: 26.5 +/- 41.5 Infants without SBI: 18.6 +/- 21.7 P<0.001 Temperature, C Infants with SBI: 38.4 +/- 0.8 Infants without SBI: 38.5 +/- 1.0 P=0.178 Diagnoses: Presumed viral syndrome= 166 (inc. URI= 61) Documented viral illness= 163 (inc. 7 with bacteruria and 1 with bacteruria and bacteremia) SBI= 44 (inc. 4 bacteremia and 41 bacteruria) Bronchiolitis= 29 (inc. RSV= 20) Otitis media= 25 Gastroenteritis= 15 (inc. rotavirus= 4) Pneumonia= 15 Aseptic meningitis= 5 (inc. enterovirus= 4) Immunisation fever= 4 Cellulitis= 3	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
2004 **Source of funding** Not reported	- Children whose families chose not to participate.		paediatrician. - Discharged patients with positive blood cultures were contacted and instructed to return to the PED for re-evaluation and subsequent management. Computerized hospital records were used to obtain duration of inpatient stays and ultimate diagnoses and were monitored for return visits to the PED within 14 days, regardless of the chief complaint. - The data were analysed using SPSS 12.0 for Windows. Independent t test comparison of means for potential SBI indicators was used.	Abscess= 2 Closed head injury= 2 Dehydration= 1 Impetigo= 1 Intussusception= 1 Omphalitis= 1 Varicella= 1 Number of diagnoses exceeds number of children in the trial because of concurrent diagnoses	
Full citation Zorc,J.J., Levine,D.A., Platt,S.L., Dayan,P.S., Macias,C.G., Krief,W., Schor,J., Bank,D., Shaw,K.N., Kuppermann,N., Multicenter RSV-SBI Study Group of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics., Clinical and demographic factors associated with urinary tract infection in young febrile infants, Pediatrics, 116, 644-648, 2005 **Ref Id** 118725 **Country/ies where the study was carried out**	**Sample size** n=1025 **Characteristics** <u>Age:</u> </= 60 days <u>Gender:</u> Not reported <u>Ethnicity:</u> White (26%) Black (22%) Hispanic/Latino (42%) Asian (7%) Other/Unknown (3%) **Inclusion criteria** All febrile (>/=38C) infants who were </=60 days of age and seen at any of the 8 paediatric emergency departments	**Interventions** Yale observation scale Maximum temperature >39C	**Details** - Physicians who evaluated the patients in the ED performed a standard history and physical examination on all enrolled patients, including completion of a Yale Observation Scale score to assess ill appearance. - Clinical factors analysed included age </=28 days, female gender, circumcision status, ill appearance (YOS>10), height of fever and white race. - Standardized laboratory evaluations were also performed. - A positive urinalysis was defined as a trace or greater result for leukocyte esterase and/or nitrite on dipstick or >/=white blood cells per high-power field on a standard microscopic examination. UTI was defined as the growth of a single known pathogen with colony counts meeting 1 of 3 criteria 1) >/=1000cfu/mL for urine cultures obtained by suprapubic aspiration 2) >/=50000cfu/mL from a catheterized specimen or 3) >/=10000cfu/mL from a catheterized specimen in association with a positive urinalysis. - The rate of UTI for each hypothesized variable was compared using the x^2 test and odds ratios with	**Results** 1005 had a urine culture test performed: 91 had a UTI 914 did not have a UTI <u>OR for predicting urinary tract infection</u> Ill appearance (YOS >10): With UTI= 4/91 Without UTI= 67/914 OR 0.6 (0.2-1.6) Maximum temperature >39C (vs. <39): With UTI= 34/91 Without UTI= 175/914 OR 2.5 (1.6-4.0)	**Limitations** One third of eligible infants were not enrolled and missed patients had a lower rate of UTI than enrolled patients. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
USA **Study type** A multicentre, prospective cross-sectional study **Aim of the study** To identify clinical and demographic factors associated with UTI in febrile infants who are </=60 days of age using a prospective multicentre cohort. **Study dates** October 1999-March 2001 **Source of funding** This study was supported in part by research grants from Roche Pharmaceuticals and Medimmune Pharmaceuticals. The study was also supported in part by General Clinical Research Center National Institutes of Health National Center for Research Resources GRANT MO1 RR00096	from October through March 1999-2001 **Exclusion criteria** Infants who had received antibiotics within 48 hours of ED presentation or when a parent or guardian refused consent.		95%CI's were calculated. Multiple logistic regression analysis with UTI as the outcome variable was also performed.		
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Thompson,M., Coad,N., Harnden,A., Mayon-	n=700	- Temperature	- All children attending the Pediatric assessment unit (PAU) were triaged by a nurse on arrival. This	Temperature >/=39C	- Comparison of the diagnostic

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
White,R., Perera,R., Mant,D., How well do vital signs identify children with serious infections in paediatric emergency care?, Archives of Disease in Childhood, 94, 888-893, 2009 **Ref Id** 119151 **Country/ies where the study was carried out** UK **Study type** Prospective cohort study **Aim of the study** To determine whether vital signs identify children with serious infections, and to compare their diagnostic value with that of the Manchester triage score (MTS) and National Institute for Health and Clinical Excellence (NICE) traffic light system of clinical risk factors. **Study dates** Not reported	**Characteristics** Age: 3 months-16 years Gender: Male (53.9%) Female (46.1%) Ethnicity: White (73.1%) Asian (12.4%) **Inclusion criteria** - Children aged 3 months-16 years attending the Pediatric Assessment Unit at the University Hospital Coventry and Warwickshire NHS Trust with an acute infection suspected by the parents, referring clinician or triage nurse. **Exclusion criteria** - Children with diseases liable to cause repeated serious bacterial infection (including haematological malignancies, iatrogenic immunosuppression), and infections resulting from penetrating trauma.	>/=39C	assessment included identifying the presenting complaint, measurement of vital signs and conscious level, together with the Manchester triage score (MTS). - The MTS system assigned children to four categories based on the maximum delay before further assessment: emergency (0 minutes), very urgent (10 minutes), urgent (60 minutes) and standard/non-urgent (120 minutes). - The triage nurses assessed activity level, respiratory distress and hydration. The vital signs measured were axillary temperature, heart rate and oxygen saturations, respiratory rate and capillary refill time. - A parental questionnaire was completed on arrival at the PAU which included a check list of 22 presenting symptoms. The children's clinical features of colour, activity, level, respiratory effort, hydration, presence of neck stiffness and non-blanching rash, as well as vital signs were categorised, blind to final outcome, into the NICE traffic light classification of intermediate (amber) and high (red) risk categories. - Details of hospital admissions were obtained from the hospital medical records. For children who were either not admitted or admitted for less than 24 hours, the PAU records were looked at for evidence of another visit in the next 7 days. - A 'severity of infection' reference standard was created based on the final diagnosis made by senior paediatricians at the time of discharge from the PAU, or inpatient ward if the child was admitted. The final diagnosis was categorised by the severity of infection: 1) minor infection 2) serious infection 3) intermediate infection 4) not infection group - Associations between vital signs with severity of infection were tested using x^2 tests. Fever was defined	Serious infection: 33/108 Intermediate infection: 49/205 Minor infection: 48/339 No infection: 0/48 x^2: p<0.001 For predicting those with serious or intermediate infection vs. minor/no infection: Sensitivity, % (95%CI): 27 (22 to 32) Specificity, % (95%CI): 87 (84 to 91) +LR (95%CI): 2.1 (1.5 to 2.9) -LR (95%CI): 0.8 (0.8 to 0.9) Minor infection: conditions from which the child was expected to recover without sequelae Serious infection: conditions that were likely to be life threatening if untreated or with high chance of life-threatening complications or sequelae Intermediate infection: Conditions that were not likely to be life-threatening, but were expected to last for > 10 days or have a non-life-threatening complication No infection: Final diagnosis that was not an acute infection	accuracy of vital signs with that of the NICE traffic light system was somewhat limited as the NICE system was developed for a more limited age range (0-5 years) and because data was not available on all the 'amber' and 'red' clinical features. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Funded by the Medical Research Council as part of a programme grant in childhood infection in primary care. Researchers were independent from the funders of the study.			as >/=39C. - The combination of vital signs that provided optimum discrimination between serious and minor infection were determined. The diagnostic characteristics of the MTS were dichotomised as 1) standard vs. urgent/very urgent/emergency and 2) standard/urgent vs. very urgent/emergency		
Full citation Maniaci,V., Dauber,A., Weiss,S., Nylen,E., Becker,K.L., Bachur,R., Procalcitonin in young febrile infants for the detection of serious bacterial infections, Pediatrics, 122, 701-710, 2008 **Ref Id** 119334 **Country/ies where the study was carried out** USA **Study type** Prospective and retrospective cohort study **Aim of the study** To study the test performance of a new automated sensitive assay	**Sample size** n= 234 **Characteristics** Mean age= 50 days (+/- 24) Male= 53% Ethnicity not reported These characteristics were compared to a group of children who met the inclusion criteria but did not have PCT measurements. There were significantly more males in the non-PCT measurements cohort. There was no significant difference in age. **Inclusion criteria** =< 90 days	**Interventions** Maximum temperature Clinical impression score	**Details** The institutional review board of the hospital approved the study and informed consent process. The study was compliant with the Health Insurance Portability and Accountability Act of 1996. All subjects received clinical care as determined by the treating paediatric emergency medicine physician. All infants =< 90 days had a complete blood count with differential, blood culture, urinalysis and urine culture with samples collected through bladder catheterisation, cerebrospinal fluid (CSF) cell count, protein level, and glucose level analyses, Gram-staining, and culture, chest radiograph if pneumonia was suggested by physical examination, and stool faecal leukocyte count and culture if clinical history or physical examination suggested possible bacterial gastroenteritis (e.g. presence of bloody or heme-positive diarrhoea). During the study period, caregivers or parents of infants who were having blood drawn for clinical evaluation were approached to participate in the study, and informed consent was obtained by an attending physician for use of blood remaining after clinical tests (if ordered by the clinical team). To ensure identification of all eligible febrile infants and to assess a capture rate for the study, an electronic log of ED visits was reviewed daily. The medical record was reviewed for all infants =< 90 days of age,	**Results** 30 children (13%) had definite SBIs - 24 with UTI (21 E coli, 1 Klebsiella pneumoniae, 2 Enterococcus) , 2 with concurrent UTI and bacteraemia (E coli), 4 with bacteraemia (Group B streptococcus) 12 children had possible SBIs - 7 with UTI (2 E coli, 1 Klebsiella pneumoniae, 2 Enterococcus, 1 Staphylococcus aureus, 1 with both E coli and Enterococcus), 5 with pneumonia 192 children had no SBI There were no cases of bacterial meningitis, definite bacterial pneumonia or bacterial gastroenteritis Maximal temperature (mean): Definite SBI= 38.9C (+/- 0.72) Definite and possible SBI= 38.9 (+/- 0.67)	**Limitations** It is not clearly reported how many children were retrospectively recruited **Other information** Diagnostic tests performed in children: Blood cultures= 100% of children Urine cultures= 97% of children CSF cultures= 84% of children Chest radiographs= 37% of children

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
for procalcitonin (PCT) with febrile infants < 90 days of age without a source of infection in physical examination and to determine an optimal cut-off value for procalcitonin to identify infants at low risk of SBI **Study dates** October 2005 to March 2007 **Source of funding** Financial support from the Frederick H Lovejoy Jr MD Resident Research Fund and an American Academy of Paediatrics resident research grant	=> 38C **Exclusion criteria** Previously identified immunodeficiency or chronic disease Focal bacterial infection (other than otitis media) on physical examination Vesicoureteral reflux requiring antibiotic prophylaxis Surgery in the previous 7 days (excluding neonatal circumcision) Immunisations in the 48 hours proceeding the visit Antibiotic treatment within the previous 48 hours		regardless of chief complaint, to identify potentially missed cases. Infants' caregivers who had not been approached for consent during the ED visit were called by the treating ED physician and offered enrolment in the study (if blood had been drawn at the ED visit). In those cases, verbal consent was obtained. At the time of enrolment, the attending physician responsible for the care of the patient completed a questionnaire to assess the overall appearance of the infant on a 5 point scale (1= moribund, toxic, ill-appearing, unresponsive, and 5= perfectly healthy, interactive infant). The electronic ED medical record was reviewed for inclusion criteria such as age, history, presence of fever without a focal bacterial source on examination, triage temperature (rectal), and laboratory and radiographic results. Statistical analysis: for continuous variable, independent-sample t-tests and the nonparametric Wilcoxon rank test were used. For categorical data, Fisher's exact test or X^2 analysis was used.	No SBI= 38.6 (+/- 0.45) Definite SBI vs. no SBI: p= 0.003 Definite and possible SBI vs. no SBI: p= 0.004 Clinical impression score (median): Definite SBI= 4 Definite and possible SBI= 4 No SBI= 4 Definite SBI vs. no SBI: p= 0.22 Definite and possible SBI vs. no SBI: p= 0.42	
Full citation Olaciregui,I., Hernandez,U., Munoz,J.A., Emparanza,J.I., Landa,J.J., Markers that predict serious bacterial infection in infants under 3 months of age presenting with fever of unknown origin, Archives of Disease in Childhood, 94, 501-505, 2009	**Sample size** n= 347 **Characteristics** Age: 4-90 days Gender: Male (56%) Female (44%)	**Interventions** Hours of fever Rectal temperature Good general state	**Details** - This study included all infants between 4 and 90 days of age seen for fever (rectal temperature >38C) in the emergency department. - The SBI group included infants with: 1) microbiologically confirmed bacteremia; 2) bacterial meningitis diagnosed by positive CSF culture; 3) sepsis, established according to the criteria defined by Levy et al including documented or suspected infection and findings of inflammation such as haemodynamic instability, tissue perfusion alteration and indications of	**Results** P value comparing serious bacterial infection with minor infection for hours of fever, rectal temperature, and good general state Hours of fever (mean, SD) SBI= 18.62 (35.8) Minor infection= 13.81 (26)	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 119349 **Country/ies where the study was carried out** Spain **Study type** Retrospective cohort study **Aim of the study** To evaluate potential markers of serious bacterial infection in infants under 3 months of age presenting with fever of unknown origin. **Study dates** Children were seen in the emergency department between January 2004 and December 2006. **Source of funding** Not reported	Ethnicity: Not reported **Inclusion criteria** - Age between 4 and 90 days - Rectal temperature > 38C - No known focus of infection - A blood test performed **Exclusion criteria** - Lack of blood test - Fever more than 7 days duration - Antibiotic therapy in the 48h prior to diagnosis - The presence of any type of immunodeficiency		organ dysfunction; 4) urinary tract infection confirmed by a positive urine culture; 5) pneumonia indicated by an infiltrate on a chest x-ray; 6) bacterial gastroenteritis confirmed by a positive stool culture; 7) cellulitis with a suggestive physical examination. - Infants with negative cultures or with improvement despite no antibiotic treatment were included in the non-SBI group. The subgroup of more invasive bacterial infection included cases of bacteremia, sepsis, and bacterial meningitis. - Demographic, personal, clinical, physical examination, and laboratory data were recorded. Two subgroups of infants were defined according to duration of fever greater or less than 12 hours. - Appropriate statistical tests were performed: student t test for comparing means of normally distributed parameters and x^2 test when comparing the distribution of categorical variables between SBI and non-SBI.	P =0.26 Rectal temperature (mean, SD) SBI= 38.23 (0.82) Minor infection= 38.28 (0.64) P =0.58 Good general state SBI= 65/82 (79%) Minor infection= 220/265 (83%) P =0.60 Diagnoses in SBI group: UTI= 69 Occult bacteraemia= 5 Cellulitis= 2 (1 with bacteraemia) Sepsis= 4 (2 with bacteraemia) Acute bacterial gastroenteritis= 1 (with bacteraemia) Pneumonia= 1 Diagnoses in non-SBI group: Viral infections (viral meningitis, viral gastroenteritis, or respiratory tract infection)= 74 Infections of probably viral aetiology (negative cultures and spontaneous resolution of the condition)= 191	
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Thayyil,S., Shenoy,M., Hamaluba,M., Gupta,A., Frater,J., Verber,I.G., Is	n=72	- McCarthy score <9	- All children had full blood count, CRP, PCT, blood cultures, chest X-ray, urine culture and a clinical	McCarthy score <9	No serious

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
procalcitonin useful in early diagnosis of serious bacterial infections in children?, Acta Paediatrica, 94, 155-158, 2005 **Ref Id** 119373 **Country/ies where the study was carried out** UK **Study type** Prospective observational study **Aim of the study** To compare diagnostic accuracy of procalcitonin for early diagnosis of serious bacterial infection (SBI) in children presenting with fever and no focus of infection. **Study dates** January 2003-September 2003 **Source of funding** North Tees and Hartlepool R&D Department	**Characteristics** Age: 1-36 months **Inclusion criteria** - Children with fever without localizing signs [FWLS] (>39C) aged 1-36 months **Exclusion criteria** - Children who had taken antibiotics in the past 72 hours - Immune deficient children - Children who had fever for more than 7 days		scoring at admission. - Selected cases had CSF examination, PCR, throat swab and nasopharyngeal aspirate. - Isolation of the pathogenic organism from a normally sterile body fluid/tissue was considered as the gold standard for diagnosing SBI. - Children were classified into one of three categories depending on the clinical and laboratory data, i.e. SBI, possible bacterial infection (no pathogenic organism isolated; however, child received antibiotics for 24-48h, until culture results available), viral or possible viral infection (isolation of virus and/or uneventful recovery without antibiotics). - Power calculations suggested that 70 children needed to be enrolled to give 90% power, at the 5% level of significance, to detect a difference in sensitivity of 15% or more between CRP and PCT, assuming a 10% incidence of SBI in FWLS. - SPSS was used for statistical analyses. To test statistical significance, the Mann-Whitney U and Kruskal-Wallis tests were used.	Sensitivity: 87.5 Specificity: 67.2 NPV: 97.7 PPV: 25.9 LR+: 0.19 (1.6%) LR-: 2.7 (21%)	limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bleeker,S.E., rksen-Lubsen,G., Grobbee,D.E., Donders,A.R., Moons,K.G., Moll,H.A., Validating and updating a prediction rule for serious bacterial infection in patients with fever without source, Acta Paediatrica, 96, 100-104, 2007 **Ref Id** 120084 **Country/ies where the study was carried out** Netherlands **Study type** Prediction model study **Aim of the study** To externally validate and update a previously developed rule for predicting the presence of serious bacterial infections in children with fever without apparent source **Study dates** Not reported however subjects were prospectively enrolled between July 2000	**Sample size** n=381 (Derivation set n=231 Validation set n=150) **Characteristics** VALIDATION SET Age: Median=0.6 years SD=0.8 Gender: Male (57%) Female (43%) Ethnicity: Not reported DERIVATION SET Age: Median=0.8 years SD=0.8 Gender: Male (53%) Female (47%) Ethnicity: Not reported **Inclusion criteria** - Patients aged 1-36 months referred by their general practitioner for the evaluation of fever without apparent source to the emergency departments of two	**Interventions** Duration of fever History of vomiting Ill clinical appearance Chest-wall retractions +/- tachypnoea Poor peripheral circulation History of decreased urinary output Changed crying pattern Temperature at examination Pale skin	**Details** - Patients aged 1-36 months presenting with fever without source (FWS) were prospectively enrolled. Serious bacterial infection was defined as the presence of bacterial meningitis, sepsis or bacteraemia, pneumonia, urinary tract infection, bacterial gastroenteritis, osteomyelitis or ethmoiditis. A follow up period of at least 2 weeks was used to rule out the possibility of a missed diagnosis of SBI. - Stepwise multivariable logistic regression analysis yielded a final prediction rule for serious bacterial infection including two subsequent models: the 'clinical model' based on patient history and physical examination characteristics and the 'clinical + lab model' including additional laboratory characteristics - To ensure the enrolment of all children with FWS, the emergency department logs and the patient classification system, in which the patients' main reason for encounter is classified, were checked - For each patient, the risk of having an SBI was predicted with the prediction rule. To determine the generalisability of the prediction rule, the predictive accuracy (calibration and discrimination) of the prediction rule was quantified. Calibration refers to the agreement between the predicted risks and the observed frequencies of SBI-this was tested with the Hosmer-Lemeshow test where a significant result indicates poor calibration. Discrimination reflects the ability of the prediction rule to discriminate those with a SBI from those without and was studied by the ROC area. Subsequently, the prediction rule was updated using all available data of the patients with fever without source.	**Results** Validation of the clinical model from Bleeker (2001) using a new group: ROC= 0.60 (95% CI 0.49 to 0.70) Predictors of SBI **Duration of fever (median, SD)** SBI absent= 2.6 days (SD 2.3) SBI present= 2.5 days (SD 2.6) Univariate analysis OR 1.1 (95% CI 1.01 to 1.21) Multivariate analysis Regression coefficient= 0.79 OR 2.2 (95% CI 1.2 to 4.1) **Changed crying pattern** SBI absent= 151/282 (54%) SBI present= 39/99 (39%) Univariate analysis OR 0.6 (95% CI 0.4 to 0.9) Multivariate analysis not reported **History of vomiting** SBI absent= 87/282 (31%) SBI present= 49/99 (50%)	**Limitations** The updated rule was tested using a cohort made up of the original data with new data added **Other information** This study is linked with Bleeker et al (2001)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and September 2001 **Source of funding** The Health Care Insurance Counsel of the Netherlands	paediatric teaching hospitals in The Netherlands between 1996-1998. (Fever without apparent source was defined as a body temperature >/= 38C for which no clear cut focus could be identified after evaluation by the general practitioner or history taking by the paediatrician). **Exclusion criteria** - Patients not referred by a general practitioner, or with immune deficiencies			Univariate analysis OR 2.2 (95% CI 1.4 to 3.5) Multivariate analysis Regression coefficient= 0.52 OR 1.7 (90% CI 1.1 to 2.6) **History of decreased urinary output** SBI absent= 72/282 (26%) SBI present= 27/99 (27%) Univariate analysis OR 1.1 (95% CI 0.7 to 1.8) Multivariate analysis not reported **Ill clinical appearance** SBI absent= 128/282 (49%) SBI present= 63/99 (64%) Univariate analysis OR 2.1 (95% CI 1.3 to 3.4) Multivariate analysis Regression coefficient= 0.45 OR 1.6 (90% CI 1.0 to 2.4) **Body temperature at physical examination (median, SD)** SBI absent= 39.3C (SD 0.9) SBI present= 39.7C (SD 1.1) Univariate analysis OR 1.18 (95% CI 0.93 to 1.49) Multivariate analysis not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Poor peripheral circulation SBI absent= 31/282 (11%) SBI present= 26/99 (26%) Univariate analysis OR 2.9 (95% CI 1.6 to 5.2) Multivariate analysis Regression coefficient= 0.7 OR 2.0 (90% CI 1.1 to 3.6) **Pale skin** SBI absent= 41/282 (15%) SBI present= 28/99 (28%) Univariate analysis OR 2.3 (95% CI 1.3 to 4.0) Multivariate analysis not reported **Chest wall retractions** SBI absent= 19/282 (7%) SBI present= 24/99 (24%) Univariate analysis OR 4.4 (95% CI 2.3 to 8.5) Multivariate analysis not reported **Chest-wall retractions +/- tachypnoea** Multivariate analysis Regression coefficient= 1.18 OR 3.3 (90% CI 1.8 to 6.0)	
Full citation Ghotbi,F., Shiva,F., An	**Sample size**	**Interventions** - Seizure >24 hr of	**Details** - 254 previously healthy children aged 6 months to 5	**Results**	**Limitations** No serious

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
assessment of the necessity of lumbar puncture in children with seizure and fever, JPMA - Journal of the Pakistan Medical Association, 59, 292-295, 2009 **Ref Id** 120309 **Country/ies where the study was carried out** Iran **Study type** Case control study **Aim of the study** To assess whether meningitis could be recognised using readily available clinical information. **Study dates** From 2002 to 2006 **Source of funding** Not reported	n=254 **Characteristics** Age: 6 months to 5 years (mean=19.3 months) Gender: Male (54%) Female (46%) Ethnicity: Not reported **Inclusion criteria** Children aged 6 months to 5 years Hospitalized in the paediatric ward at Taleghani Teaching Hospital associated with Shaheed Beheshti University of Medical Sciences. **Exclusion criteria** Not reported	onset of fever - Repeated seizures (>1 episode) - Prolonged seizure (>15 min) - Lethargy - Irritability - Vomiting - Nuchal rigidity - Bulging fontanel - Headache - Toxicity - Drowsiness - Coma	years were brought consecutively to the paediatric department of a teaching hospital after their first fever-associated-seizure. Lumbar puncture was performed in all cases. - Children with seizure and fever and meningitis served as cases and those with fever and seizure, but no meningitis served as controls. - Factors compared in the two groups were: age, lethargy, irritability, vomiting, nuchal rigidity, bulging fontanel, headache, drowsiness, toxicity, coma, complex seizure, and prior antibiotic use. - Various other laboratory tests were carried out - All data was analysed using Fisher exact test, p value and odds ratio. Using Woolf approximation, a 95% confidence interval was obtained. - The child was considered as a case of meningitis if WBC > 10/cu mm, Gram stain positive for bacteria, and/or a positive CSF culture, sugar level in CSF of < 40mg/dL and/or protein > 80 mg/dl	- Seizure >24 hr of onset of fever Meningitis: 9/12 (75%) No meningitis: 15/242 (6%) P value: <0.0001 Odds ratio (95%CI): 45.4 (11.11 to 185.5) - Repeated seizures (>1 episode) Meningitis: 6/12 (50%) No meningitis: 53/242 (22%) P value: 0.0354 Odds ratio (95%CI): 3.566 (1.1-11.5) - Prolonged seizure (>15 min) Meningitis: 3/12 (25%) No meningitis: 24/242 (10%) P value: 0.1228 Odds ratio (95%CI): 3.028 (0.0766-11.955) - Lethargy Meningitis: 5/12 (42%) No meningitis: 13/242 (5%) P value: <0.0006 Odds ratio not reported	limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				- Irritability Meningitis: 7/12 (58%) No meningitis: 34/242 (14%) P value: <0.0008 Odds ratio not reported - Vomiting Meningitis: 8/12 (67%) No meningitis: 0/242 (0%) P value: <0.0001 Odds ratio not reported - Nuchal rigidity Meningitis: 4/12 (33%) No meningitis: 0/242 (0%) P value: <0.0001 Odds ratio not reported - Bulging fontanel Meningitis: 1/12 (8%) No meningitis: 0/242 (0%) P value: <0.047 Odds ratio not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				- Headache Meningitis: 2/12 (17%) No meningitis: 1/242 (<1%) P value: <0.006 Odds ratio not reported - Toxicity Meningitis: 4/12 (33%) No meningitis: 8/242 (3%) P value: <0.0012 Odds ratio not reported - Drowsiness Meningitis: 3/12 (25%) No meningitis: 0/242 (0%) P value: <0.0001 Odds ratio not reported - Coma Meningitis: 1/12 (8%) No meningitis: 0/242 (0%) P value: <0.047 Odds ratio not reported	
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Fouzas,S., Mantagou,L., Skylogianni,E., Varvarigou,A., Reactive thrombocytosis in febrile young infants with serious bacterial infection, Indian Pediatrics, 47, 937-943, 2010 **Ref Id** 136091 **Country/ies where the study was carried out** Greece **Study type** Retrospective study **Aim of the study** To estimate the incidence of reactive thrombocytosis among febrile young infants and to assess the utility of platelet count as a potential predictor of serious bacterial infection. **Study dates** Children admitted to paediatric care unit between 1 January 2005 and 31 December 2008 **Source of funding**	n=408 **Characteristics** Age: 29-89 days Gender: Male (54%) Female (46%) Ethnicity: Not reported **Inclusion criteria** - All infants 29 to 89 days of age, admitted with rectal temperature >38C without a focus of infection **Exclusion criteria** Infants who had fever for more than 72 hours, and had received antibiotics or vaccination within 48 hours of presentation	Duration of fever Fever on admission	- The case-records of infants aged 29 to 89 days admitted to a tertiary care paediatric unit were reviewed. All patients had sepsis evaluation. Lumbar puncture for CSF analysis and culture, as well as stool culture and chest radiographs were obtained at the discretion of the attending paediatrician. - Serious bacterial infection was defined as occult bacteremia, urinary tract infection, bacterial meningitis, pneumonia, bacterial enteritis and infection of soft tissue or bones. Urinary tract infection was defined as a single known pathogen growth >/= 1000 cfu/mL of urine obtained by suprapubic needle aspiration or >/=100,000cfu/mL of urine obtained by urethral catheterization. Pneumonia was defined as the presence of a focal infiltrate on chest radiograph as interpreted by the attending radiologist. - Data were analysed using SPSS 15.0. Non parametric data are presented as medians with interquartile ranges. Differences between the groups were assessed for statistical significance using either the Mann Whitney U or chi-squared test, as appropriate. - Individual differences between nonparametric variables were evaluated by the Kruskal-Wallis multiple-comparison z-value test with Bonferroni correction. The overall performance of individual parameters in predicting SBI was assessed by ROC curve analyses and area under the curve comparisons.	P value of duration of fever and fever on admission comparing those with SBIs and those without Duration of fever: Non-SBI= 14 hours (6 to 27) SBI= 14 hours (6 to 29) P=0.49 Fever on admission: Non-SBI= 38.5C (38.1 to 38.8) SBI= 38.5C (38.1 to 39.0) P=0.22	No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
None					
Full citation Gomez,B., Mintegi,S., Benito,J., Egireun,A., Garcia,D., Astobiza,E., Blood culture and bacteremia predictors in infants less than three months of age with fever without source, Pediatric Infectious Disease Journal, 29, 43-47, 2010 **Ref Id** 136096 **Country/ies where the study was carried out** Spain **Study type** Retrospective cross-sectional study **Aim of the study** To assess the rate of bacteraemia in febrile infants less than 3 months of age admitted to the Pediatric Emergency Department of a tertiary hospital, to describe the bacteria isolated in these children, and to analyse any factors related to a higher probability of having	**Sample size** n= 1018 **Characteristics** Male/Female= 585/433 Age distribution: =< 30 days= 243 31 to 60 days= 417 61 to 90 days= 358 Time elapsed between detection of fever and attending the ED (available for 91.6% of patients) =< 3 hours= 360 =< 6 hours= 501 Ethnicity not reported **Inclusion criteria** < 90 days Measured temperature => 38C at home or on arrival	**Interventions** Highest temperature detected General appearance	**Details** All subjects received clinical care as determined by the emergency physician. Algorithm for the management of infants less than 3 months old with fever without source recommends urine dipstick testing, CBC, CRP, blood culture, and urine culture for all children. Gram stain of urine is not routinely performed. Performing a lumbar puncture, including Gram stain, bacterial culture, viral culture and enterovirus polymerase chain reaction is considered on an individual basis. An electronic log of Pediatric Emergency Department visits was reviewed monthly by a paediatric emergency physician to ensure proper identification of all potentially eligible febrile infants and to assess the capture rate for the study. Electronic medical records were reviewed and the following data recorded for each patient: demographics (age, gender, month when care was provided), medical history, time elapsed between moment when fever was first detected and when the infant was brought to the hospital, temperature registered at home and at the ED, whether the child appeared ill upon arrival or not, symptoms and findings on physical examination, results of any tests performed, treatment received, diagnosis, site of care, and evolution. Well-appearing was defined as a normal paediatric assessment after being evaluated by a paediatric emergency physician during the first hour after attending the ED. Appearance, respiratory and circulatory items had to be classified as normal for infants to be classified as well-appearing, and data had to be reflected on the patient's charts. Continuous data were compared using the X2 test or the Fisher exact test probability test.	**Results** 198 had SBI (UTI= 172, occult bacteraemia= 9, UTI and bacteraemia= 8, bacterial meningitis= 4, sepsis= 2, cellulitis= 2, acute otitis media= 1) 820 had no SBI A true bacterial pathogen grew in 23 of the 1018 blood culture cases (9 Escherichia coli, 4 Streptococcus pneumoniae, 3 Group B Neisseria meningitidis, 3 Enterococcus faecalis, 2 Streptococcus agalactiae, 1 Klebsiella pneumoniae, 1 Staphylococcus aureus) - occult bacteraemia, UTI and bacteraemia, bacterial meningitis and sepsis <u>Not well-appearing:</u> Positive blood culture (occult bacteraemia, UTI and bacteraemia, bacterial meningitis or sepsis)= 6/23 Negative blood culture (no occult bacteraemia, UTI and bacteraemia, bacterial meningitis or sepsis)= 42/995 <u>Well-appearing:</u> Positive blood culture (occult bacteraemia, UTI and bacteraemia, bacterial meningitis or sepsis)= 17/23 Negative blood culture (no occult bacteraemia, UTI and bacteraemia, bacterial meningitis or sepsis)= 953/995 Temperature data is reported, however the	**Limitations** No serious limitations **Other information** Most of these children were included in Gomez (2012), which reports different symptoms and signs. Temperature data is reported, however the data is not reported clearly enough to be used by the NCC-WCH

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
a positive blood culture. **Study dates** September 2003 to August 2008 **Source of funding** None reported	(Patients with fever and mild nasal congestion) **Exclusion criteria** Patients with a diarrheal process or certain respiratory symptoms/signs (such as tachypnea, breathing difficulties, wheezing, grunting, nasal flaring, retractions, rhonchi, rales, focal areas of decreased breath sounds) were not included. Patients in whom the history and/or the physical examination performed upon arrival in the Pediatric Emergency Department allowed the origin of fever to be identified were excluded.			data is not reported clearly enough to be used by the NCC-WCH	
Full citation Bin,Salleeh H., McGillivray,D., Martin,M., Patel,H., Duration of fever affects the likelihood of a positive bag urinalysis or catheter culture in young children, Journal of Pediatrics, 156, 629-633, 2010 **Ref Id** 138200	**Sample size** n=818 **Characteristics** Age: 3-36 months Gender: Not reported Ethnicity: Not reported	**Interventions** Duration of fever	**Details** - A prospective cohort study of infants and children aged 3-36 months presenting to a tertiary care paediatric ED with documented fever without source (FWS) between April 2005 and September 2007 was conducted. - Bag urinalyses are ordered mainly by the nurse at triage or by a physician following assessment of a febrile, non-toilet-trained, nontoxic child age 3-36 months with FWS. Urine bags are applied to the perineal area after cleansing with water. No bag urine specimens are sent for culture.	**Results** RR for positive bag urine culture based on duration of fever - Patients with fever of 3 days duration had the highest proportion of positive urinalyses. On day 1, 14.8% (35/237) of the urinalyses were positive, compared with 26.4% (43/163) on day 3 (RR=1.8; 95%CI=1.2-2.7; P=0.004). When duration of fever was dichotomized into </=2 days versus >/=3 days of fever, the children with longer duration of fever had a greater risk of having a positive bag urinalysis (14.6%	**Limitations** Appropriateness of using a bag urinalysis - a negative bag screen does not invariably rule out UTI. Children with a negative bag urinalysis did not undergo the gold standard

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Canada **Study type** Prospective cohort study **Aim of the study** To test the hypothesis that there will be a clinically significant rise in the proportion of positive bag urinalyses and catheter cultures in young children with increasing duration of fever. **Study dates** April 2005-September 2007 **Source of funding** Funded by the Montreal Children's Hospital Research Institute	**Inclusion criteria** - 3 to 36 months - Fever without source - Rectal temperature >/=38C recorded in ED or by parental report - Bag urinalysis initiated by the nurse at triage or requested by the child's physician. **Exclusion criteria** - Toxic appearance - Known renal disease - Immunocompromised status - The need to proceed directly to catheterization - Antibiotic use in the previous 10 days		- An automated Clinitek 100/200 analyzer and Multistix 10 SG reagent strip urine dipsticks were used for analysis of leukocyte esterase and nitrites. A positive result was defined as greater than trace amounts of leukocyte esterase or a positive nitrite test. A positive catheter urine culture was defined as growth of >/=10^7CFU/L or >/=10^4CFU/mL of a single pathogenic organism. Multiple organisms were not considered positive even if >10^7 CFU/L were present. - If the bag dipstick urinalysis was positive, then a catheter sample was obtained for urinalysis and culture. If the bag dipstick urinalysis was negative, then no further testing was done. - Data collected included age, sex, race, circumcision status in males, highest reported fever by the parents or documented in the ED, duration of fever, laboratory results on the bag urine specimen, and the culture results obtained on all catheter urine specimens. - FWS was defined as either fever with no identified etiology following a detailed history and physical examination, or fever with equivocal etiology where the potential source of fever was either nonspecific (e.g., early viral illness) or of low clinical severity (e.g., mild gastroenteritis or otitis media). - Fever was defined as a rectal temperature >/=38C recorded in ED or by parental report. - The primary outcome was the proportion of positive bag urinalyses by fever duration (<1 day, 2, 3, 4 or >/=5 days of fever). The secondary outcome was the proportion of positive urine catheter cultures by duration of fever. - A sensitivity analysis was conducted to evaluate the significance of those infants who had a positive bag urinalysis but did not have a urine culture. The x^2 test was used to compare the proportions of positive bag	[64/438] vs. 23.2% [88/380]; RR=1.6; 95%CI=1.2-2.1; P=0.002) <u>Number of positive catheter urine cultures based on duration of fever</u> - The percentage of positive cultures was lowest on day 1 (4.8%; 11/229) and highest on day 3 (12.6%; 20/159) (RR=2.6; 95%CI: 1.3-5.3; P=0.005). When duration of fever was dichotomized into </=2 days versus >/=3days of fever, the children with longer duration of fever were at greater risk of having a positive bag catheter culture (5.0% [21/421] vs. 11.1% [41/367]; RR=2.2; 95%CI=1.3-3.7; P=0.001]	test for UTI (catheter urine culture). Therefore, false negative results are possible. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			urinalyses and catheter cultures for the 5 different durations of fever, the proportions for fever of 1 day versus 3 days and the proportions for the dichotomised time periods. The level of significance used was p<0.05. Relative risks and confidence intervals were calculated. The statistical program used was SPSS version 11.0.		
Full citation Stathakis,T., Acworth,J.P., Barnett,A.G., Prediction tool for bacteraemia in children aged 3-36 months, Emergency Medicine Australasia, 19, 353-358, 2007 **Ref Id** 139421 **Country/ies where the study was carried out** Australia **Study type** Retrospective chart review **Aim of the study** To determine which parameter is the most reliable predictor of bacteremia in children aged 3-36 months and to develop a simple tool to assess risk of bacteremia. **Study dates**	**Sample size** n=1488 **Characteristics** Age: 3-36 months Gender: Male (52.4%) Female (47.6%) Ethnicity: Not reported **Inclusion criteria** Children aged 3-36 months presenting to triage with a history of fever, and who (at the discretion of the treating physician) had blood taken for both blood culture and full blood count. (Fever defined as a core temperature of 38C or above measured by	**Interventions** Temperature at presentation	**Details** A retrospective review was performed on patients aged 3-36 months who presented to a paediatric ED between July 1999 and April 2004. Children with a febrile illness who had blood culture and full blood count performed were included in the study. Fever was defined as a core temperature of 38C or above measured by tympanic thermometer. Data were collected from the pathology database and Emergency Department Information System. Variables examined were age, sex, and temperature at presentation, white cell count, neutrophil count and blood culture result. Multiple regression analysis was used to determine the independent predictors of bacteremia. Non-linear regression analysis was applied to explore alternative patterns of bacteremia risk.	**Results** Mean temperature: Bacteraemia-positive= 39.0C (SD 0.9) Bacteraemia-negative= 38.8C (SD 1.0) OR: 1.06 (95%CI: 0.74, 1.51) P=0.80	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
July 1999-April 2004 **Source of funding** Not reported	tympanic thermometer). **Exclusion criteria** Children with leukaemia or other causes of immunodeficiency. Cases in which temperature was not recorded upon presentation.				
Full citation Batra,P., Gupta,S., Gomber,S., Saha,A., Predictors of meningitis in children presenting with first febrile seizures, Pediatric Neurology, 44, 35-39, 2011 **Ref Id** 139426 **Country/ies where the study was carried out** India **Study type** Retrospective case review **Aim of the study** To determine the	**Sample size** n=199 **Characteristics** <u>Age:</u> 6-18 months <u>Gender:</u> Not reported <u>Ethnicity:</u> Not reported **Inclusion criteria** - Children aged 6-18 months presenting with a first episode of seizures with fever, admitted to the paediatric casualty wards of the Guru Teg Bahadur Hospital in Delhi. **Exclusion criteria**	**Interventions** - Complex febrile seizure - Duration of seizures >/= 30 minutes - Postictal drowsiness - Neurologic deficit	**Details** - This study was a retrospective case review of patients with a first episode of seizures with fever, admitted to the paediatric casualty wards of the Guru Teg Bahadur Hospital in India. - Clinical and investigative profiles of all patients were analysed. These patients were further classified as manifesting simple and complex febrile seizures, using their records and the definition given by the National Institutes of Health. - This further classification was undertaken to help in studying the prevalence of meningitis in two groups separately. A diagnosis of meningitis was rendered on the basis of cerebrospinal fluid cell count, cerebrospinal fluid protein and cerebrospinal fluid sugar levels. - A positive cerebrospinal fluid Gram stain and cerebrospinal fluid culture were considered the gold standard for a diagnosis of meningitis. A diagnosis of first febrile seizure was confirmed in patients who fulfilled the criteria of the National Institutes of Health. - Statistical analysis was performed using SPSS	**Results** <u>Simple febrile seizure</u> Meningitis: 1/5 (20%) Non-meningitis: 115/194 (59.2%) P value, sensitivity, specificity, PPV, NPV and accuracy not reported <u>Complex febrile seizure</u> Meningitis: 4/5 (80%) Non-meningitis: 79/194 (40.8%) P value: 0.163 Sensitivity: 80% Specificity: 59.2% Positive predictive value: 57.1% Negative predictive value: 59.2% Accuracy: 59.7% <u>Duration of seizures <15 minutes</u> Meningitis: 1/5 (20%) Non-meningitis: 121/194 (62.3%) P value, sensitivity, specificity, PPV, NPV	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
prevalence of bacterial meningitis in children aged 6-18 months presenting with first febrile seizures. Also, to assess the clinical predictors of bacterial meningitis in such children. **Study dates** Not reported however subjects were admitted to the paediatric casualty wards between January 2003 and December 2008 **Source of funding** Not reported	- Children with a known seizure disorder (one or more previous seizures without fever), underlying chronic neurologic condition (hydrocephalus, brain tumour, neurocutaneous syndrome, or cerebral palsy), metabolic abnormalities (hypoglycemia or hypocalcemia) and incomplete records.		version 13.0. Nominal data were analysed using the Fisher exact test. Causes of fever such as upper respiratory tract infection, acute suppurative otitis media, pneumonia, and gastritis were compared between the meningitis and non-meningitis groups, using the Pearson x^2 test. P<0.05 was taken as significant.	and accuracy not reported <u>Duration of seizures 15 to 30 minutes</u> Meningitis: 0/5 (0%) Non-meningitis: 70/194 (36.1%) P value, sensitivity, specificity, PPV, NPV and accuracy not reported <u>Duration of seizures >/= 30 minutes</u> Meningitis: 4/5 (80%) Non-meningitis: 3/194 (1.5%) P value: <0.001 Sensitivity: 80% Specificity: 98.4% Positive predictive value: 57.1% Negative predictive value: 99.4% Accuracy: 97.9% <u>Postictal drowsiness</u> Meningitis: 3/5 (60%) Non-meningitis:8/194 (4.12%) P value: 0.001 Sensitivity: 60% Specificity: 95.8% Positive predictive value: 27.2% Negative predictive value: 98.9% Accuracy: 94.9% <u>Neurologic deficit</u> Meningitis: 4/5 (80%) Nonmeningitis:1/194 (0.5%) P value:<0.001 Sensitivity: 80% Specificity: 99.4% Positive predictive value: 80% Negative predictive value: 99.4%	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Accuracy: 98.9%	
Full citation Trautner,B.W., Caviness,A.C., Gerlacher,G.R., Demmler,G., Macias,C.G., Prospective evaluation of the risk of serious bacterial infection in children who present to the emergency department with hyperpyrexia (temperature of 106 degrees F or higher), Pediatrics, 118, 34-40, 2006 **Ref Id** 139513 **Country/ies where the study was carried out** USA **Study type** Cross-sectional observational study **Aim of the study** To determine: 1) the risk of serious bacterial infection in children with hyperpyrexia 2) whether clinical presentation can identify	**Sample size** n=103 **Characteristics** <u>Age:</u> Children < 18 years <u>Gender:</u> Male (55.3%) Female (44.7%) <u>Ethnicity:</u> Black (47.6%) Hispanic (36.9%) White (11.7%) Asian (3.9%) **Inclusion criteria** Children < 18 years presenting to a paediatric emergency department during a 2-year period (24 September 1998 to 24 September 2000) with rectal temperatures of >/= 106 F (41.1 C) **Exclusion criteria** None	**Interventions** Duration of fever Viral symptoms: Rhinorrhea Vomiting Diarrhoea Injected conjunctivae Any viral symptom	**Details** All children presenting to the paediatric ED with a rectal temperature >/= 106F (41.1C) were enrolled. All subjects were assessed for the following viral symptoms: rhinorrhea, vomiting, diarrhoea, sweating and conjunctival injection. History, physical examination, complete blood cell counts, blood cultures and nasopharyngeal viral cultures were obtained on all of the patients. Statistical analyses were performed using SPSS for Windows. Overall frequencies of subject ages, gender, ethnicity and viral symptoms were calculated with 95% confidence intervals. Overall frequencies of final diagnoses were also calculated with 95%CIs. Odds ratios and 95%CIs were used to explore the association among age, duration of fever, underlying medical condition, WBC count, absolute neutrophil count and viral symptoms with bacterial or viral illness.	**Results** <u>Children with hyperpyrexia</u> Febrile illness without positive cultures (no serious bacterial or viral illness) = 60/103 (58.3%) Viral illness with positive culture= 21/103 (20.4%) Bacterial illness with positive culture= 19/103 (18.4%) Positive viral and bacterial culture= 1/103 (1%) (Remaining two children - 1 had neuroleptic malignant syndrome in response to a ventriculoperitoneal shunt, 1 had new onset systemic lupus erythematosus from renal stents and recurrent pyelonephritis) Of those with febrile illness with negative cultures, 13 had CXR with a lobar infiltrate compatible with pneumonia, and 11 diagnoses with otitis media by physical examination (2 had both otitis media and pneumonia). <u>Duration of fever and viral symptoms as predictors of bacterial illness in children with hyperpyrexia</u> <u>Duration of fever (hours):</u> <24 Ref 24 to <48 Odds ratio: 0.30 (0.07-1.26) >48 Odds ratio: 1.04 (0.35-3.12) <u>Viral symptoms:</u> Rhinorrhea OR (95%CI): 0.27 (0.09-0.76) Vomiting OR (95% CI): 0.76 (0.26-2.18) Diarrhoea OR (95% CI): 3.93 (1.27-12.19) Injected conjunctivae OR (95% CI): 0.43	**Limitations** No serious limitations **Other information** Viral illnesses were: adenovirus (n=7), picornavirus (n=1), enterovirus (n=2), RSV (n=6), influenza A (n= 5), cytomegalovirus (n=1), and parainfluenza 3 (n=1)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
hyperpyrexic patients at risk for serious bacterial infection **Study dates** September 1998 to September 2000 **Source of funding** US Public Health Service grant				(0.05-3.63) Any viral symptom OR (95% CI): 0.33 (0.12-0.95)	
Full citation Brent,A.J., Lakhanpaul,M., Thompson,M., Collier,J., Ray,S., Ninis,N., Levin,M., MacFaul,R., Risk score to stratify children with suspected serious bacterial infection: Observational cohort study, Archives of Disease in Childhood, 96, 361-367, 2011 **Ref Id** 139672 **Country/ies where the study was carried out** UK **Study type** Observational cohort study **Aim of the study**	**Sample size** n=1951 (with temperature measurement n=1716) **Characteristics** Age: Median-19months (Range-1 month to 15 years) Gender: Male (55.4%) Female (44.6) Ethnicity: Not reported **Inclusion criteria** - Children with acute infection	**Interventions** Temperature 35.0-36.4C Temperature 36.5-37.5C Temperature 37.5-38.4C Temperature >/=38.5C	**Details** - An observational cohort study of children presenting with suspected infection to the Queen's Medical Centre Emergency Department in Nottingham between September 2000 and March 2001, and September 2001 and March 2002 was conducted. (with the exception of neonates and children requiring immediate emergency resuscitation at presentation) - A triage nurse recorded vital signs prior to assessment by emergency department clinical staff. All clinical data were directly entered onto a standard proforma. Study clinicians checked the data for completeness, resolved data gaps and inconsistencies by re-review of the clinical notes, and recorded additional clinical data on children who were admitted. - Children who re-attended hospital within 1 week of discharge from either the emergency department or the ward were identified from the electronic patient register, their notes reviewed, and final diagnoses and SBI classification amended in the light of their second presentation. A consultant paediatrician re-reviewed the patient records of all those admitted to check accuracy of the data.	**Results** Univariable associations between clinical variables and risk of serious bacterial infection 1716 children had their temperature measured 74 of those who had their temperature measured had SBI Temperature 35.0-36.4C With SBI= 9/74 Without SBI= 417/1716 Odds ratio (95%CI): 0.82 (0.37-1.82) Temperature 36.5-37.5C With SBI= 20/74 Without SBI= 760/1716 Odds ratio (95%CI:) 1.00 (NR)	**Limitations** Risk of incorporation bias, since clinicians are not blind to the admission clinical variables studied, which are likely to influence admission decisions; inclusion of clinical and laboratory data from the entire admission in assigning outcome is likely to only partly mitigate this bias. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To derive and validate a clinical score to risk stratify children presenting with acute infection **Study dates** Children presented to the Emergency department between September 2000 and March 2001, and September 2001 and March 2002. **Source of funding** Andrew J Brent is supported by a Wellcome Trust research training fellowship (081697). The authors wish to thank the Well Child Medical Charity for their funding of the studies in Nottingham and of this study.	**Exclusion criteria** - Children for whom data were insufficient to confidently assign outcome, or who had missing dates of birth.		- Automated measurements were used for temperature (tympanic thermometer), pulse rate, blood pressure and pulse oximetry. Tachypnoea, tachycardia and hypotension were defined according to UK Advanced Pediatric Life Support guidelines; children for whom no blood pressure recordings were available were assumed not to be hypotensive for the purpose of the analysis. - Data collected routinely on all children included level of consciousness, capillary refill time, hydration status, and presence and type of rash. - SBI was defined a priori as admission to hospital plus any of the following (in the absence of an alternative non-infective or non-bacterial diagnosis to explain the clinical and laboratory findings): positive bacterial cultures from blood or another normally sterile site in the appropriate clinical context, radiological signs of pneumonia, clinical meningitis plus a cerebrospinal fluid polymorphonuclear leukocytosis, acute febrile purpura, deep collection requiring intravenous antibiotics +/- surgical drainage, a white blood cell count >/=20 x 10^9/l, a C reactive protein >/=120mg/l, or a final diagnosis of septic arthritis, osteomyelitis, empyema or mastoiditis. - Analyses were performed using Stata version 10. The distribution of each variable was summarised with respect to SBI, and crude OR derived. The sensitivity, specificity, PPV, NPV and likelihood ratios were reported for each variable.	<u>Temperature 37.5-38.4C</u> With SBI= 17/74 Without SBI= 188/1716 Odds ratio (95%CI): 1.86 (1.01-3.43) <u>Temperature >/=38.5C</u> With SBI= 28/74 Without SBI= 276/1716 Odds ratio (95% CI): 4.10 (2.39-7.05) <u>Predictive value of clinical variables for serious bacterial infection</u> <u>>/=37.5C</u> With SBI= 45/74 Without SBI= 464/1716 Sensitivity,% (95%CI): 60.8 (48.8-72.0) Specificity,% (95%CI): 64.5 (62.2-66.7) PPV,% (95%CI): 6.5 (4.8-8.6) NPV,% (95%CI): 2.4 (1.6-3.4) LR+(95%CI): 1.7 (0.65-4.5) LR-(95%CI): 0.61 (0.23-1.61) <u>>/=38.5C</u> With SBI= 28/74 Without SBI= 276/1716	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Sensitivity,% (95%CI): 37.8 (26.8-49.9) Specificity,% (95%CI): 84.8 (83.1-86.4) PPV,% (95%CI): 9.2 (6.2-13.0) NPV,% (95%CI): 97.1 (96.1-97.9) LR+(95%CI): 2.5 (1.1-5.7) LR-(95%CI): 0.73 (0.32-1.7)	
Full citation Shettigar,C.G., Rao,D., Hegde,P., Soans,S., Routine urine culture in febrile young children, Journal of Clinical and Diagnostic Research, 5, 452-455, 2011 **Ref Id** 139687 **Country/ies where the study was carried out** India **Study type** Prospective observational cohort study **Aim of the study** To assess the usefulness of the routine urine culture	**Sample size** n=334 **Characteristics** Age: less than 5 years of age Gender: Male (57%) Female (43%) Ethnicity: Not reported **Inclusion criteria** Age less than 5 years of age who were admitted to the paediatric ward with an axillary temperature of >/=37.4C within 24 hours of admission	**Interventions** Temperature (37.4C to 38.3C, 38.4C to 39.3C, >39.3C)	**Details** A detailed history and clinical examination was performed in all cases to find the cause of fever, with special emphasis being given to the symptoms of UTI. Necessary investigations were carried out to find the cause of fever. The perineum and genitalia were washed with soap and water. A freshly voided, clean catch, mid-stream urine sample was collected in sterile containers for urinalysis and culture. Urine was collected by catheterization in those children who could not void urine within 24 hours after admission, after taking aseptic precautions. Urinalysis was done within half an hour and the same specimen was immediately transported to the Department of Microbiology for urine culture. The urine was cultured on CLED agar and Mac Conkey's agar by using a 0.001ml calibrated wire loop and the plates were observed for 48 hours. Colony counts which were >50 x $10^{3/}$ml and >10^{5}/ml of single organisms in catheterised and mid-stream urine samples respectively, were considered to be diagnostic of urinary tract infections.	**Results** Total number of cases and culture positive cases (for UTI) in each temperature range Temperature 37.4C-38.3C With serious illness: 6/27 Without serious illness: 126/307 Total number of cases: 132 Culture positive cases: 6/132 (5%) Culture negative cases: 126/132 Temperature 38.4C-39.3C With serious illness: 12/27 Without serious illness= 132/307 Total number of cases: 144 Culture positive cases: 12/144 (8%) Culture negative cases: 132/144 Temperature >39.3C With serious illness: 9/27 Without serious illness: 47/307 Total number of cases: 58 Culture positive cases: 9/58 (16%)	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
in febrile young children **Study dates** October 2009-September 2010 **Source of funding** Not reported	**Exclusion criteria** Those children who had received antibiotics or had undergone bladder catheterization within 48 hours prior to the admission		Urine cultures were repeated 48 hours after starting the appropriate antibiotic therapy if there was no clinical response and once again, after the completion of the antibiotic course, to detect the bacteriological response to the treatment. Each case of UTI was treated and followed up as per standard protocols. Correlations between the variables were analysed by using the Chi-square test, the t-test and the z-test wherever necessary. P values <0.05 were taken as statistically significant.	Culture negative cases: 47/58 No statistically significant difference in the number of culture positive cases amongst the three groups	
Full citation Craig,J.C., Williams,G.J., Jones,M., Codarini,M., Macaskill,P., Hayen,A., Irwig,L., Fitzgerald,D.A., Isaacs,D., McCaskill,M., The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children: prospective cohort study of 15 781 febrile illnesses, BMJ, 340, c1594-, 2010 **Ref Id** 139929 **Country/ies where the study was carried out** Australia **Study type**	**Sample size** n= 12807 **Characteristics** Age: Children under 5 years, presenting with a febrile illness between 1 July 2004 and 30 June 2006 Gender: 44.1% male, 55.9% female Ethnicity: Not reported **Inclusion criteria** - Consecutive children under 5 years of age presenting to the emergency department of The Children's Hospital at Westmead with a febrile illness	**Interventions** • Urinary symptoms • General appearance • Fluid intake • Highest temperature • Chronic disease • Felt hot • Meningococcal vaccine • Capillary refill time • Crying • Elevated heart rate • Chest crackles • Pneumococcal vaccine • Breathing difficulty • Elevated respiratory rate • Infectious contacts	**Details** - Doctors at the emergency department of The Children's Hospital were asked to fill an electronic records system which standardised the mandatory entry of 40 symptoms and signs for all children presenting with febrile illness - Doctors were also asked to estimate the probability that their patient had any of 10 potential diagnoses - Children were then diagnosed as having a serious bacterial infection (urinary tract infection, pneumonia and bacteraemia), clinically diagnosed infection, or no bacterial infection using standard radiological and microbiological tests - All eligible febrile children were followed up until they fulfilled the case definition for serious bacterial infection or until the fever had resolved for >/= to 24 hours - A model was then developed according to the clinical symptoms and signs data in the electronic records and the case definition. A preliminary analysis was used to select variables for inclusion in the multinomial model. The selected variables were then fitted in a multinomial logistic regression model and variables that were no	**Results** Serious bacterial infection (UTI, pneumonia or bacteraemia)= 1140 illnesses in 1054 children UTI= 543 Pneumonia= 533 Bacteraemia= 64 Osteomyelitis= 12 Septic arthritis= 8 Meningitis= 6 Presentations with fever without SBI= 14,641 illnesses in 11,753 children Age group 0-3 months Frequency: 756 Pneumonia: 33 UTI: 93 Bacteraemia: 17 >3 months-<3yrs Frequency: 11653 Pneumonia: 356 UTI: 394	**Limitations** The results are reported per illness rather than per child - some children had more than one illness. Microbiological and radiological verification was not present in all children - some bacterial infections may not have been detected before they spontaneously resolved **Other information** A double

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Prospective cohort study **Aim of the study** To evaluate current processes by which young children presenting with a febrile illness but suspected of having serious bacterial infection are diagnosed and treated, and to develop and test a multivariable model to distinguish serious bacterial infections from self-limiting non-bacterial illnesses. **Study dates** 1 July 2004-30 June 2006 **Source of funding** The National Health and Medical Research Council of Australia	between 1 July 2004 and 30 June 2006 - Febrile illness was defined as any illness with one or more of the following elements: a measured axillary temperature of >/= 38C; parental report of a temperature of >/= 38C measured at home within the previous 24 hours; a parental report that the child 'felt hot' in the previous 24 hours; or a presenting problem related to fever (10th revision of the international classification of diseases, Australian modification codes R50, R50.0, R50.1, R50.9 and R56.0), as determined by a triage nurse **Exclusion criteria** - Children transferred to The Children's Hospital from another hospital - Children with cancer and transplant recipients because disease frequency, clinical evaluation, and threshold for treatment are substantially different from those of children with normal immune	• Male • Abnormal chest sounds • Respiratory symptoms • Diarrhoea • Abnormal ear, nose and throat signs • Cough • Focal bacterial infection • Bulging fontanelle • Rash • Wheeze • Age • Stridor	longer statistically significant were removed using backward elimination - The performance of the model was assessed for each type of serious bacterial infection by constructing a receiver operating characteristic (ROC) curve - The clinical diagnoses estimated by clinicians were compared against the model to test the accuracy of clinician judgment when attempting to identify bacterial infection in children with fever	Bacteraemia: 35 <u>>3yrs-<5yrs</u> Frequency: 3392 Pneumonia: 144 UTI: 56 Bacteraemia: 12 <u>Respiratory symptoms</u> <u>No</u> Frequency: 4425 All SBI: 344/1140 Pneumonia: 42/533 UTI: 273/543 Bacteraemia: 29/64 No SBI: 4081/14641 <u>Yes</u> Frequency: 11376 All SBI: 796/1140 Pneumonia: 491/533 UTI: 270/543 Bacteraemia: 35/64 No SBI: 10580/14641 <u>Diarrhoea</u> <u>No</u> Frequency: 11770 All SBI: 899/1140 Pneumonia: 417/533 UTI: 427/543 Bacteraemia: 55/64 No SBI: 10871/14641 <u>Yes</u> Frequency: 4031 All SBI: 241/1140 Pneumonia: 116/533 UTI: 116/543	reference standard test was used - children were classified as 'negative' for SBI if all reference standard tests that were done were negative (this was the case in 25% of children) and if, on follow-up, a parent reported resolution of the child's illness by days 10 to 14.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	function			Bacteraemia: 9/64 No SBI: 3790/14641 <u>Urinary symptoms</u> <u>No</u> Frequency: 15482 All SBI: 1115/1140 Pneumonia: 552/533 UTI: 500/543 Bacteraemia: 63/64 No SBI: 14367/14641 <u>Yes</u> Frequency: 319 All SBI: 55/1140 Pneumonia: 11/533 UTI: 43/543 Bacteraemia: 1/64 No SBI: 264/14641 <u>General appearance</u> <u>Well</u> Frequency: 6456 All SBIs: 291/1140 Pneumonia: 101/533 UTI: 182/543 Bacteraemia: 8/64 No SBI: 6165/14641 <u>Mildly unwell</u> Frequency: 7874 All SBIs: 595/1140 Pneumonia: 288/533 UTI: 278/543 Bacteraemia: 29/64 No SBI: 7279/14641	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Moderately unwell Frequency: 1407 All SBIs: 225/1140 Pneumonia: 129/533 UTI: 76/543 Bacteraemia: 20/64 No SBI: 1182/14641 Very unwell Frequency: 64 All SBI: 29/1140 Pneumonia: 15/533 UTI: 7/543 Bacteraemia: 7/64 No SBI: 35/14641 Breathing difficulty No Frequency: 13644 All SBI: 849/1140 Pneumonia: 291/533 UTI: 507/543 Bacteraemia: 51/64 No SBI: 12795/14641 Yes Frequency: 2157 All SBI: 291/1140 Pneumonia: 242/533 UTI: 36/543 Bacteraemia: 13/64 No SBI: 1866/14641 Bulging fontanelle No Frequency: 9297 All SBI: 755/1140 Pneumonia: 302/533 UTI: 414/543	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Bacteraemia: 39/64 No SBI: 8542/14641 <u>Yes</u> Frequency: 42 All SBI: 8/1140 Pneumonia: 2/533 UTI: 4/543 Bacteraemia: 2/64 No SBI: 34/14641 <u>Closed</u> Frequency: 6462 All SBI: 377/1140 Pneumonia: 229/533 UTI: 125/543 Bacteraemia: 23/64 No SBI: 6085/14641 <u>Chronic disease</u> <u>No</u> Frequency: 13802 All SBI: 878/1140 Pneumonia: 392/533 UTI: 437/543 Bacteraemia: 49/64 No SBI: 12924/14641 <u>Yes</u> Frequency: 1999 All SBI: 262/1140 Pneumonia: 141/533 UTI: 106/543 Bacteraemia: 15/64 No SBI: 1737/14641 <u>Cough</u> <u>No</u> Frequency: 7286	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				All SBI: 483/1140 Pneumonia: 70/533 UTI: 374/543 Bacteraemia: 39/64 No SBI: 6803/14641 <u>Yes</u> Frequency: 8515 All SBI: 657/1140 Pneumonia: 463/533 UTI: 169/543 Bacteraemia: 25/64 No SBI: 7858/14641 <u>Chest crackles</u> <u>No</u> Frequency: 14487 All SBI: 921/1140 Pneumonia: 342/533 UTI: 522/543 Bacteraemia: 57/64 No SBI: 13566/14641 <u>Yes</u> Frequency: 1314 All SBI: 219/1140 Pneumonia: 191/533 UTI: 21/543 Bacteraemia: 7/64 No SBI: 1095/14641 <u>Crying</u> <u>No</u> Frequency: 10585 All SBI: 656/1140 Pneumonia: 335/533 UTI: 295/543 Bacteraemia: 26/64	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				No SBI: 9929/14641 <u>Yes</u> Frequency: 5216 All SBI: 484/1140 Pneumonia: 198/533 UTI: 248/543 Bacteraemia: 38/64 No SBI: 4732/14641 <u>Abnormal ENT</u> <u>No</u> Frequency: 7230 All SBI: 660/1140 Pneumonia: 269/533 UTI: 344/543 Bacteraemia: 47/64 No SBI: 6570/14641 <u>Yes</u> Frequency: 8571 All SBI: 480/1140 Pneumonia: 264/533 UTI: 199/543 Bacteraemia: 17/64 No SBI: 8091/14641 <u>Felt hot</u> <u>No</u> Frequency: 1209 All SBI: 50/1140 Pneumonia: 26/533 UTI: 20/543 Bacteraemia: 4/64 No SBI: 1159/14641 <u>Yes</u> Frequency: 14592 All SBI: 1090/1140	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Pneumonia: 507/533 UTI: 523/543 Bacteraemia: 60/64 No SBI: 13502/14641 <u>Fluid intake</u> <u>Usual</u> Frequency: 7344 All SBI: 469/1140 Pneumonia: 200/533 UTI: 244/543 Bacteraemia: 25/64 No SBI: 6875/14641 <u>Small decrease</u> Frequency: 6332 All SBI: 480/1140 Pneumonia: 231/533 UTI: 220/543 Bacteraemia: 29/64 No SBI: 5852/14641 <u>Moderate decrease</u> Frequency: 2088 All SBI: 183/1140 Pneumonia: 100/533 UTI: 74/543 Bacteraemia: 9/64 No SBI: 1905/14641 <u>None</u> Frequency: 37 All SBI: 8/1140 Pneumonia: 2/533 UTI: 5/543 Bacteraemia: 1/64 No SBI: 29/14641 <u>Abnormal chest sounds</u>	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				No Frequency: 13319 All SBI: 806/1140 Pneumonia: 245/533 UTI: 506/543 Bacteraemia: 55/64 No SBI: 12513/14641 Yes Frequency: 2482 All SBI: 334/1140 Pneumonia: 288/533 UTI: 37/543 Bacteraemia: 9/64 No SBI: 2148/14641 Elevated heart rate No Frequency: 8954 All SBI: 475/1140 Pneumonia: 197/533 UTI: 259/543 Bacteraemia: 19/64 No SBI: 8479/14641 Yes Frequency: 6847 All SBI: 665/1140 Pneumonia: 336/533 UTI: 284/543 Bacteraemia: 45/64 No SBI: 6182/14641 Elevated respiratory rate No Frequency: 13587 Pneumonia: Not reported UTI: Not reported Bacteraemia: 57/64	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				No SBI: 13530/14641 <u>Yes</u> Frequency: 2214 Pneumonia: Not reported UTI: Not reported Bacteraemia: 7/64 No SBI: 2207/14641 <u>Focal bacterial infection</u> <u>No</u> Frequency: 14297 All SBI: 1042/1140 Pneumonia: 483/533 UTI: 508/543 Bacteraemia: 51/64 No SBI: 13255/14641 <u>Yes</u> Frequency: 1504 All SBI: 98/1140 Pneumonia: 50/533 UTI: 35/543 Bacteraemia: 13/64 No SBI: 1406/14641 <u>Infectious contacts</u> <u>No</u> Frequency: 11451 All SBI: 828/1140 Pneumonia: 346/533 UTI: 434/543 Bacteraemia: 48/64 No SBI: 10623/14641 <u>Yes</u> Frequency: 4350 All SBI: 312/1140 Pneumonia: 187/533	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				UTI: 109/543 Bacteraemia: 16/64 No SBI: 4038/14641 Rash No Frequency: 13023 All SBI: 1006/1140 Pneumonia: 485/533 UTI: 475/543 Bacteraemia: 46/64 No SBI: 12017/14641 Yes Frequency: 2778 All SBI: 134/1140 Pneumonia: 48/533 UTI: 68/543 Bacteraemia: 18/64 No SBI: 2644/14641 Capillary refill time <2secs Frequency: 15083 All SBI: 1012/1140 Pneumonia: 469/533 UTI: 494/543 Bacteraemia: 49/64 No SBI: 14071/14641 2-3secs Frequency: 670 All SBI: 111/1140 Pneumonia: 60/533 UTI: 42/543 Bacteraemia: 9/64 No SBI: 559/14641 >3secs	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Frequency: 48 All SBI: 17/1140 Pneumonia: 4/533 UTI: 7/543 Bacteraemia: 6/64 No SBI: 31/14641 <u>Stridor</u> <u>No</u> Frequency: 15520 All SBI: 1127/1140 Pneumonia: 522/533 UTI: 541/543 Bacteraemia: 64/64 No SBI: 14393/14641 <u>Yes</u> Frequency: 281 All SBI: 13/1140 Pneumonia: 11/533 UTI: 2/543 Bacteraemia: 0/64 No SBI: 268/14641 <u>Highest recorded temperature (C)</u> <u><38</u> Frequency: 3444 All SBI: 169/1140 Pneumonia: 93/533 UTI: 67/543 Bacteraemia: 9/64 No SBI: 3275/14641 <u>38 to 38.9C</u> Frequency: 5634 All SBI: 353/1140 Pneumonia: 147/533 UTI: 184/543 Bacteraemia: 22/64	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				No SBI: 5281/14641 <u>39 to 39.9C</u> Frequency: 5002 All SBI: 449/1140 Pneumonia: 201/533 UTI: 226/543 Bacteraemia: 22/64 No SBI: 4553/14641 <u>=> 40C</u> Frequency: 1721 All SBI: 169/1140 Pneumonia: 92/533 UTI: 66/543 Bacteraemia: 11/64 No SBI: 1552/14641 <u>Audible wheeze</u> <u>No</u> Frequency: 14783 All SBI: 1047/1140 Pneumonia: 451/533 UTI: 534/543 Bacteraemia: 62/64 No SBI: 13736/14641 <u>Yes</u> Frequency: 1018 All SBI: 93/1140 Pneumonia: 82/533 UTI: 9/543 Bacteraemia: 2/64 No SBI:925/14641	
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Morris,C.M., Tefuarani,N., Ripa,P., Laki,R., Vince,J.D., Urinary tract infection in infants and young children	n=98	Irritability	- This prospective study was carried out in the Children's Outpatients Department, Port Moresby	"Clinical signs and symptoms (irritability, diarrhoea, vomiting and abdominal pain)	Many of the diagnoses were presumptive - did not have

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
presenting with fever without a focus in Port Moresby, Papua New Guinea Medical Journal, 50, 145-151, 2007 **Ref Id** 140145 **Country/ies where the study was carried out** Papua New Guinea **Study type** Prospective study **Aim of the study** To determine the prevalence of UTI as a cause of fever without a focus in Papua New Guinean children **Study dates** 20-week period in 2003. **Source of funding** Not reported	**Characteristics** Age: <36 months Gender: Male (56%) Female (44%) Ethnicity: Not reported **Inclusion criteria** - Age of less than 36 months - An axillary temperature of >37.2C - The absence of a focus elicited by history and physical examination - No antibiotic treatment in the previous week **Exclusion criteria** Not reported	Diarrhoea Vomiting Abdominal pain	General Hospital over a 20-week period in 2003. - Children meeting the inclusion criteria were referred by the nursing and medical staff to the main investigator. After informed verbal consent, a further history, physical examination and investigation were performed, and further management determined. - All children had a full blood examination including haemoglobin and white blood count, a blood smear for malaria parasites, and urine testing, with dipstick for leukocyte esterase and nitrite, microscopy and culture. Blood cultures were taken when practicable, depending on availability of blood culture bottles and amount of blood collected. A lumbar puncture and cerebrospinal fluid examination were done only if clinically indicated. - Urine was collected non-invasively, by midstream collection in the older cooperative children and by clean catch in the younger children. Urine, once obtained, was tested by dipstick for leukocyte esterase and nitrite and taken immediately to the microbiology laboratory where microscopy and culture using standard culture methods were carried out. - A pure growth with a colony count of $>10^5$ organisms/ml was taken as the gold standard of diagnosis of a urinary infection. - Study children who returned to the clinic within the next two days with additional symptoms were classified accordingly. - A diagnosis of non-specific viral infection was made if no cause was apparent after investigation, if there was a lymphocyte predominance on white cell count and if the child did not return with additional symptoms. Diagnoses of lower respiratory tract infection and gastroenteritis were made on the basis of the subsequent development of suggestive clinical	were not predicative of UTI." Diagnoses: Non-specific viral infection= 31 Lower respiratory tract infection= 11 Urinary tract infection= 9 Malaria= 7 Meningitis= 4 Bacteraemia= 1 Others= 21 Unknown= 14 Total= 98	access to the tests that would confirm viral infection **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			symptoms and signs. - Data were entered into Epi Info 6 and SPSS 10.0 software programs for analysis. Sensitivity and specificity were calculated for the various urine tests.		
Full citation Rabasa,A.I., Gofama,M.M., Urinary tract infection in febrile children in Maiduguri north eastern Nigeria, Nigerian Journal of Clinical Practice, 12, 124-127, 2009 **Ref Id** 140146 **Country/ies where the study was carried out** Nigeria **Study type** Prospective cohort study **Aim of the study** To study the prevalence of UTI in febrile children presenting to the University of Maiduguri Teaching Hospital, where like other tropical environments, fever is a common cause of hospital visit. **Study dates** November 2004-October	**Sample size** n=145 **Characteristics** Age: 1 month to 60 months (5 years) Gender: Male (61.4%) Female (38.6%) Ethnicity: Not reported **Inclusion criteria** Children aged 1 to 60 months who presented with fever (axillary temperature >/=37.5C). **Exclusion criteria** Children younger than one month or older than 5 years and those with axillary temperature less than 37.5C.	**Interventions** Crying on micturition/dysuria Vomiting	**Details** - Following a history and full clinical examination, clean catch urine (CCU) specimen was collected into a universal sterile container and analysed within 30 minutes of collection. Where CCU specimen was not available, a suprapubic bladder aspiration (SPA) was performed. - A sample was placed onto MacConkey's agar and cysteine Lactose electrolyte deficient medium and incubated for 18-24 hours, at 37.1C. All organisms were identified by standard laboratory techniques. All isolates were tested for antimicrobial sensitivity using the disc diffusion method. - Urinalysis was also done immediately on a portion of the freshly obtained urine sample by dipstick method. Number of pus cells were counted using x40 objective. Significant pyuria defined as pus cells > 5 per high power field of urine. - Urine culture was considered positive in the presence of pure growth of $>10^5$ cfu/mL of the freshly obtained urine from clean catch specimens, or presence of any growth from a urine specimen obtained by suprapubic bladder aspiration. - Categorical variables were compared between patients using the Chi-squared test. Fisher's exact test was used where appropriate. P value<0.05 was considered to be significant.	**Results** Chi squared and p values for comparing children with and without UTI Crying on micturition/dysuria Children with UTI= 2/20 (10%) Children without UTI= 18/125 (14%) X^2 value: 0.28 P >0.05 Vomiting Children with UTI= 12/20 (60%) Children without UTI= 50/125 (40%) X^2 value: 2.8 P >0.05	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
2005 **Source of funding** Not reported					
Full citation Owusu-Ofori,A., Agbenyega,T., Ansong,D., Scheld,W.M., Routine lumbar puncture in children with febrile seizures in Ghana: should it continue?, International Journal of Infectious Diseases, 8, 353-361, 2004 **Ref Id** 140347 **Country/ies where the study was carried out** Ghana **Study type** Prospective observational cohort **Aim of the study** To determine the positive yield of lumbar punctures in a setting where routine lumbar puncture is routinely carried out and to determine if any other parameter could help differentiate bacterial	**Sample size** n= 608 **Characteristics** Age: 3 months-15 years Gender: Male (55.4%) Female (44.6%) Ethnicity: Not reported **Inclusion criteria** - Children aged 3 months to 15 years hospitalised at the Komfo Anokye Teaching Hospital in Kumasi, Ghana between July and August 2000 **Exclusion criteria** - Patients who had repeated lumbar punctures, who were transferred to another unit or who left the hospital against medical advice.	**Interventions** Temperature < 37.5C or >/= 37.5C	**Details** - The study was conducted at the paediatric unit of the Komfo Anokye Teaching Hospital, Ghana. - Children who had an LP on admission were recruited into this study. Their physical examination findings at the time of the LP were recorded after obtaining their history. The doctor performing the LP stated the indication for which the LP was carried out and all laboratory findings were noted. - Bacterial meningitis was defined as having a CSF white cell count of >0.005 x 10^9/l, protein of >4g/dl, CSF glucose of <1.0mmol/l with or without bacteria seen on Gram stain or culture. - Febrile convulsion was defined as a child with an age range of 6 months to 6 years, presenting with a febrile seizure for which there was no identifiable cause for the fever.	**Results** Temperature < 37.5 With serious illness (malaria or meningitis): 29/114 Without serious illness ('others' or febrile convulsion): 8/38 All patients= 71 Cerebral malaria= 7 Severe malaria= 13 Malaria= 4 Febrile convulsion= 3 Bacterial meningitis= 5 Others= 39 Temperature >/= 37.5 With serious illness (malaria or meningitis): 85/114 Without serious illness ('others' or febrile convulsion): 30/38 All patients= 115 Cerebral malaria= 23 Severe malaria= 21 Malaria= 27 Febrile convulsion= 26 Bacterial meningitis= 14 Others= 4	**Limitations** Children who had multiple diagnoses were classified as 'others', rather than in each diagnostic group. Those with septicaemia, UTI and pneumonia were also classified as 'others'. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
meningitis from various other diagnoses of children who presented with a febrile seizure. **Study dates** July -August 2000 **Source of funding** Not reported	- Known cases of meningitis who had an LP elsewhere before they were referred to this teaching hospital.				
Full citation Newman,T.B., Bernzweig,J.A., Takayama,J.I., Finch,S.A., Wasserman,R.C., Pantell,R.H., Urine testing and urinary tract infections in febrile infants seen in office settings: the Pediatric Research in Office Settings' Febrile Infant Study, Archives of Pediatrics and Adolescent Medicine, 156, 44-54, 2002 **Ref Id** 140625 **Country/ies where the study was carried out** USA **Study type** Prospective observational	**Sample size** n=3066 n= 1666 had a urinalysis or urine culture on the day of first examination **Characteristics** <u>Age:</u> </= 3 months <u>Gender:</u> Male (53%) Female (47%) <u>Ethnicity:</u> White (70%) African American (8%) Asian or Pacific Islander (2%) Hispanic (15%) Other, unknown or missing (5%) **Inclusion criteria**	**Interventions** Increased sleepiness Decreased urination Decreased social interaction Decreased feeding Decreased activity Increased vomiting Duration of fever Maximum temperature Well or minimally ill appearance Moderately ill	**Details** - This study was conducted in practices participating in the American Academy of Pediatrics' practice-based research network, PROS. - 573 practitioners from 219 practices enrolled eligible patients to the study between February 28, 1995 and April 25, 1998. - The PROS practitioners and their office staffs recorded clinical and demographic data on standard forms. The study protocol required that the initial physical examination results, diagnostic impression, and assessment of overall severity of illness be recorded before the results of any laboratory tests were available. Results of many components of the history and physical examination could be indicated by checking appropriate boxes on the data collection form. - For the most important data items (initial temperature, age, sex, and final outcome), most missing, ambiguous, or suspicious data items were obtained through inquiries to individual PROS practitioners. The data collection form included the dates of urine cultures but not of urinalyses, The authors considered urine testing to have been done on the date of the urine culture, if available. For infants for whom no urine culture date	**Results** <u>Odds ratios and P values for a UTI for each sign/symptom</u> Increased sleepiness With UTI= 54/161 Without UTI= 450/1505 OR= 1.2 P=0.34 Decreased urination With UTI= 27/161 Without UTI= 206/1505 OR=1.3 P=0.28 Decreased social interaction With UTI= 38/161 Without UTI= 396/1505 OR=0.9 P=0.46 Decreased feeding With a UTI= 59/161 Without a UTI= 563/1505 OR=1.0 P=0.85	**Limitations** Some eligible infants who presented to PROS practitioners were not enrolled and so it is possible that such infants were more, equally or less ill than infants in the study. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
cohort study **Aim of the study** To determine the predictors and results of urine testing of young febrile infants seen in office settings. **Study dates** February 28, 1995 and April 25, 1998 **Source of funding** This study was supported by grant RO1 HS06485 from the Agency for Health Care Policy and Research, Rockville, Md; and grant MCJ-177022 from the Health Resources and Services Administration Maternal and Child Health Bureau, Rockville.	- Infants were </=3 months - Infants had axillary, rectal or tympanic temperatures >/=38C in the office or in the previous 24 hours at home - Infants were initially examined by a PROS practitioner **Exclusion criteria** Not reported	appearance Very ill appearance URI or runny nose Otitis media or abnormal TMs Respiratory distress Chest findings Cough Conjunctivitis Colour pale, mottled, or cyanotic Not alert Dehydrated Weak or high-pitched cry Inconsolable No smile	was provided, the date of the initial examination was used. - Practitioners followed up all infants and recorded each interaction until the infants had recovered from the acute illness. - Odds ratios and P values of various signs and symptoms for UTI were calculated.	Decreased activity With a UTI= 28/161 Without a UTI= 277/1505 OR=0.9 P=0.75 Increased vomiting With UTI= 24/161 Without a UTI= 266/1505 OR=0.8 P=0.38 Duration of fever >/=24h With UTI= 30/161 Without UTI= 149/1505 OR=2.1 P=0.001 Maximum temperature 38.0 to 38.4 With UTI= 37/161 Without UTI= 570/1505 Reference value for OR Maximum temperature 38.5C-38.9C With UTI= 60/161 Without UTI= 548/1505 OR=1.7 P=0.01 Maximum temperature 39.0-39.4C With UTI= 33/161 Without UTI= 272/1505 OR=1.9 P=0.01 Maximum temperature >/=39.5C With UTI= 31/161 Without UTI= 115/1505 OR=4.2 P<0.001	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Well or minimally ill appearance With UTI= 97/161 Without UTI= 956/1505 Reference value for OR Moderately ill appearance With UTI= 55/161 Without UTI= 492/1505 OR=1.1 P=0.58 Very ill appearance With UTI= 6/161 Without UTI= 38/1505 OR=1.6 P=0.32 URI or runny nose With UTI= 8/161 Without UTI= 155/1505 OR=0.5 P=0.03 Otitis media or abnormal Tympanic membranes With UTI= 7/161 Without UTI= 126/1505 OR=0.5 P=0.07 Respiratory distress With UTI= 10/161 Without UTI= 208/1505 OR=0.4 P=0.007 Chest findings With UTI= 3/161 Without UTI= 75/1505 OR=0.4	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				P=0.08 Cough With UTI= 1/161 Without UTI= 25/1505 OR=0.4 P=0.31 Conjunctivitis With UTI= 1/161 Without UTI= 13/1505 OR=0.7 P=0.75 Colour pale, mottled, or cyanotic With UTI= 15/161 Without UTI= 127/1505 OR=1.1 P=0.70 Not alert With UTI= 31/161 Without UTI= 373/1505 OR=0.7 P=0.12 Dehydrated With UTI= 9/161 Without UTI= 130/1505 OR=0.6 P=0.18 Weak or high-pitched cry With UTI= 17/161 Without UTI= 182/1505 OR=0.9 P=0.57 Inconsolable With UTI= 32/161 Without UTI= 441/1505	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				OR=0.6 P=0.01 No smile With UTI= 49/161 Without UTI= 546/1505 OR=0.8 P=0.14	
Full citation Bleeker,S.E., Moons,K.G., rksen-Lubsen,G., Grobbee,D.E., Moll,H.A., Predicting serious bacterial infection in young children with fever without apparent source, Acta Paediatrica, 90, 1226-1232, 2001 **Ref Id** 140639 **Country/ies where the study was carried out** Netherlands **Study type** Retrospective chart review **Aim of the study** To design a clinical rule to predict the presence of a serious bacterial infection in children with fever without apparent source	**Sample size** n=231 **Characteristics** <u>Age:</u> Mean: 1.1 years, Range: 1 to 36 months <u>Gender:</u> Male 53%, Female 47% <u>Ethnicity:</u> Not reported **Inclusion criteria** - 1 to 36 months old - acute fever without apparent source (including suspected sepsis) **Exclusion criteria** Patients not referred by a general practitioner Patients referred from	**Interventions** Duration of fever History of poor micturition History of vomiting Temperature <36.7C or >/=40C at examination Chest wall retractions +/- tachypnoea Poor peripheral circulation Poor intake Purulent nasal discharge in history or at examination Decreased consciousness	**Details** - Data were collected by reviewing standardized medical records - Documented data from patient history and physical examination included age, gender, gestation age, body weight, body temperature, duration of fever(body temperature >/=38 degrees), coughing, vomiting, diarrhoea, micturition, intake, crying pattern, vital signs, clinical appearance, fontanelle and information on ear-nose-throat, skin and the respiratory-, circulatory- and abdominal tract. Data from laboratory tests were collected from the computer-documented hospital information system. - The final diagnosis for each patient was determined either by a reference standard (cultures of blood, spinal fluid, urine, stool positive for a pathogen) or based on a consensus diagnosis - Outcome diagnosis was the presence or absence of a serious bacterial infection (bacterial meningitis, sepsis or bacteraemia, pneumonia, urinary tract infection, bacterial gastroenteritis, osteomyelitis or ethmoiditis) - A 2 week follow up period was the standard for ruling out the possibility of a missed diagnosis of serious bacterial infection - Variables with a univariate p-value of 0.15 or less were subsequently entered into a stepwise multivariate	**Results** <u>Univariate analysis</u> Vomiting: SBI= 64/173 (37%) No SBI= 33/58 (57%) p < 0.15 Poor micturition: SBI= 57/173 (33%) No SBI= 12/58 (21%) p < 0.15 Poor intake: SBI= 63/173 (36%) No SBI= 15/58 (26%) p < 0.15 Duration of fever (mean days, SD): SBI= 2.6 (2.2) No SBI= 3.2 (2.8) p < 0.15 Purulent nasal discharge in history or at examination: SBI= 35/173 (20%) No SBI= 27/58 (47%) p < 0.15 Temperature < 36.7 C or =/> 40 C at examination:	**Limitations** No serious limitations **Other information** Odds ratios of independent predictors from laboratory tests presented in table 3 of article but not reported here as not relevant to the review

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Sophia Children's University Hospital, Rotterdam from 1996 to 1998 Juliana Children's Hospital, The Hague in 1998 **Source of funding** Financial support from The Health Care Insurance Council of The Netherlands	other hospitals Patients with immune deficiencies	Bulging fontanelle Chest-wall retractions +/- tachypnoea Crepitations Bulging abdomen	logistic regression procedure. Variables with a multivariate p-value of less than 0.10 were considered to be independent predictors of a serious bacterial infection	SBI= 53/173 (31%) No SBI= 28/58 (48%) p < 0.15 Decreased consciousness: SBI= 6/173 (4%) No SBI= 5/58 (9%) p < 0.15 Bulging fontanelle: SBI= 9/173 (5%) No SBI= 6/58 (10%) p < 0.15 Chest-wall retractions +/- tachypnoea: SBI= 9/173 (5%) No SBI= 16/58 (28%) p < 0.15 Poor peripheral circulation: SBI= 19/173 (11%) No SBI= 13/58 (25%) p < 0.15 Crepitations: SBI= 4/173 (2%) No SBI= 4/58 (7%) p < 0.15 Bulging abdomen: SBI= 10/173 (6%) No SBI= 7/58 (12%) p < 0.15 <u>Multivariate analysis</u> Duration of fever (in days): OR(90%CI): 2.5 (0.8 to 7.5) History of poor micturition:	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				OR(90%CI): 0.5 (0.3 to 1.0) History of vomiting: OR(90%CI): 2.3 (1.2 to 4.3) Temperature <36.7C or >/=40C at examination: OR(90%CI): 1.7 (0.9 to 3.0) Chest wall retractions +/- tachypnoea: OR(90%CI): 4.9 (2.3 to 10.7) Poor peripheral circulation: OR(90%CI): 1.6 (0.7 to 3.6)	
Full citation Factor,S.H., Schillinger,J.A., Kalter,H.D., Saha,S., Begum,H., Hossain,A., Hossain,M., Dewitt,V., Hanif,M., Khan,N., Perkins,B., Black,R.E., Schwartz,B., Diagnosis and management of febrile children using the WHO/UNICEF guidelines for IMCI in Dhaka, Bangladesh, Bulletin of the World Health Organization, 79, 1096-1105, 2001 **Ref Id** 140640 **Country/ies where the study was carried out** Bangladesh	**Sample size** n=669 **Characteristics** Age: 2-59 months Gender: Male (62%) Female (38%) Ethnicity: Not reported **Inclusion criteria** -Children aged 2-59 months who presented to the Dhaka Shishu Hospital (DSH) outpatient department or emergency room during daytime operating hours between September	**Interventions** Diagnostic classifications of the integrated management of childhood illness (IMCI): -General danger signs present (not able to drink or breastfeed, vomits everything, or convulsions, or abnormally sleepy or difficult to wake up) -Very severe febrile disease (fever [by history, feels hot, or axillary temperature => 37.5C] AND any general danger	**Details** - A systematic sample of children aged 2 to 59 months who presented to the Dhaka Shishu Hospital (DSH) outpatient department or emergency room during daytime operating hours between September 1994 and February 1995 were approached for enrolment in the study. - Strategies to enrich the study sample with acutely ill children were implemented at different points during the study period. These included preferential enrolment of children triaged to the emergency room by hospital personnel, children with abnormal temperatures (<35.5C or >37.5C axillary temperatures), and children with evidence of respiratory distress (noisy breathing, chest indrawing or elevated respiratory rate). - A nurse measured and recorded the weight, tactile and measured temperature, and respiratory rate for each patient. Physicians interviewed parents for a complete history, performed a physical examination of the child and recorded all findings on a standard form. - Fast respiratory rate was defined by age as >50 breaths per minute (2-11 months) or >40 breaths per	**Results** Parental report of fever for more than 3 days and measured axillary temperature of => 38C Meningitis= 5/12 Pneumonia= 60/200 Bacteraemia= 9/20 Dysentery= 4/48 Otitis media= 4/21 Bacterial skin infection= 6/46 UTI= 8/30 No bacterial infection= 44/289	**Limitations** Attempts to enrich the study population for acute disease may have resulted in the inclusion of more children with respiratory and febrile disease than might be seen in a typical clinic population. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Prospective observational study **Aim of the study** To determine whether the fever module in the WHO/UNICEF guidelines for the integrated management of childhood illness identifies children with bacterial infections in an area of low malaria prevalence. **Study dates** September 1994-February 1995 **Source of funding** This study was funded by the John Hopkins Family Health and Child Survival Cooperative Agreement with the United States Agency for International Health Development.	1994 and February 1995 **Exclusion criteria** - Children who had been seen at the DSH within the previous week, admitted to the hospital within the previous 2 weeks, or were attending the hospital for routine immunization, physiotherapy or a prearranged appointment with the hospital specialty departments (e.g.: renal, orthopaedic, cardiology).	sign, or stiff neck) -Severe pneumonia or very severe disease(cough or difficult breathing and any general danger sign, chest indrawing, or stridor in a calm child) -Pneumonia (cough or difficulty breathing and 50 breaths per minute or more in a child aged 2 to 11 months or 40 breaths per minute or more in a child aged 12 to 59 months) -Dysentery (diarrhoea and blood in the stool) -Severe complicated measles (fever [by history, feels hot, or axillary temperature => 37.5C] AND generalised rash AND cough, runny nose, or red eyes, AND any general danger sign, clouding of cornea, or deep or extensive mouth	minute (12-59 months) and abnormal temperature defined as an axillary temperature of <35.5C or >37.5C. Chest radiographs and lumbar punctures were performed as required. - Blood cultures were performed on a systematic sample of children with a history of fever in the previous 24 hours and for any child with an abnormal axillary temperature. - Other tests were ordered as required. Treatment decisions were made based on the medical history, physical examination and available laboratory data. - The frequency of fever and various other signs and symptoms in children with and without bacterial infections was measured to determine their sensitivity and specificity for identifying bacterial infections, and developed alternative fever modules using signs and symptoms found to be sensitive for bacterial infection. To evaluate these alternative modules, the overall sensitivity and specificity of the IMCI guidelines was measured for children with bacterial infections with each of these modules in place. - Data were analysed using SAS software.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		ulcers) -Mastoiditis (ear problem AND tender swelling behind the ear) -Acute ear infection (ear problem AND ear pain or ear discharge for less than 14 days or pus seen draining from the ear)			
Full citation Nielsen,H.E., Andersen,E.A., Andersen,J., Bottiger,B., Christiansen,K.M., Daugbjerg,P., Larsen,S.O., Lind,I., Nir,M., Olofsson,K., Diagnostic assessment of haemorrhagic rash and fever, Archives of Disease in Childhood, 85, 160-165, 2001 **Ref Id** 140679 **Country/ies where the study was carried out** Denmark **Study type** Propsective observational study	**Sample size** n=264, complete data available for 208 **Characteristics** <u>Age:</u> greater than 1 month and less than 16 years <u>Gender:</u> Not reported <u>Ethnicity:</u> Not reported **Inclusion criteria** - Presence of haemorrhages in the skin, irrespective of size detected at admission or during the stay in hospital - Rectal temperature	**Interventions** - Fever, median duration (h) - Coughing - Vomiting - Median temperature - Nuchal rigidity - General condition, median sum of scores - Individuals with >20 skin haemorrhages - Maximum diameter > 1mm	**Details** - Examinations were recorded on pre-printed study forms. This included information from the case history and a standardised physical examination which was repeated 6-24 hours later. - In the physical examination, special emphasis was placed on a description of the skin haemorrhages. The clinician decided whether their appearance matched none, one, or several of the 7 types which were printed on the study form. The maximum diameter of the largest haemorrhage was measured with a ruler. Their number and distribution above and below the nipple line was documented. - Various clinicopathological and microbiological tests were performed as required. - Medians were used to describe the central tendency of the various distributions. Comparisons between distributions were based on the Wilcoxon two sample test. Proportions were compared by a x^2 test with Yates's correction or by Fisher's exact test. Logistic regression was used to elucidate the diagnostic value of a number of clinical and laboratory parameters, the impact of each variable being expressed as odds ratios	**Results** 39 children had meningococcal disease 169 children had no invasive bacterial disease <u>CASE HISTORY PRIOR TO INCLUSION</u> - <u>Fever, median duration:</u> Meningococcal disease= 21 hours No invasive bacterial disease= 24 hours p value= n.s - <u>Coughing:</u> Meningococcal disease= 6/39 (15%) No invasive bacterial disease= 63/169 (37%) P < 0.05 - <u>Vomiting:</u> Meningococcal disease= 17/39 (44%) No invasive bacterial disease= 68/169 (40%) P value= n.s	**Limitations** Of the 39 patients with meningococcal disease, 29 were confirmed and 10 were probable cases **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To establish criteria for early distinction between meningococcal disease and other conditions with similar clinical features, and to identify other causes for haemorrhagic rashes accompanied by fever. **Study dates** September 1993-June 1996 **Source of funding** Supported by grants from King Christian IX and Queen Louise's Foundation and the Danish Hospital Foundation for Medical Research, Region of Copenhagen, the Faeroe Islands, and Greenland.	above 38C at some time within the 24 hours before inclusion - Age greater than 1 month and less than 16 years **Exclusion criteria** - If a child was admitted twice during the study period and fulfilled the inclusion criteria on both occasions, only the first admission was included in the study		in a model with all significant variables entered. For small probabilities, the odds ratio is approximately equal to the relative risk, which expresses the risk of being in the meningococcal disease group relative to the risk of being in the non-meningococcal disease group when the corresponding clinical sign or laboratory variable is positive.	PHYSICAL SIGNS AT INCLUSION - Median temperature: Meningococcal disease= 40C No invasive bacterial disease= 39C P < 0.01 - Nuchal rigidity: Meningococcal disease= 16/39 (41%) No invasive bacterial disease= 5/169 (3%) P < 0.001 - General condition, median sum of scores: Meningococcal disease= 6 No invasive bacterial disease= 9 P < 0.001 SKIN HAEMORRHAGES - Individuals with >20 skin haemorrhages: Meningococcal disease= 29/39 (74%) No invasive bacterial disease= 86/169 (51%) P < 0.05 - Maximum diameter > 1mm: Meningococcal disease= 37/39 (95%) No invasive bacterial disease= 37/169 (22%) P < 0.001 - Maximum diameter > 2mm: Meningococcal disease= 29/39 (74%) No invasive bacterial disease= 14/169 (8%) P < 0.001 - Universal distribution: Meningococcal disease= 36/39 (92%) No invasive bacterial disease=	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				68/169 (40%) P < 0.001 - Skin haemorrhages of types C-E: Meningococcal disease= 32/39 (82%) No invasive bacterial disease=12/169 (7%) P < 0.001 No invasive bacterial disease defined as either no bacterial cultures from blood or spinal fluid and no antibiotic treatment prior to culture, or no blood culture, but spontaneous recovery (i.e. no antibiotic treatment before or during hospitalisation)	
Full citation Hewson,P., Poulakis,Z., Jarman,F., Kerr,J., McMaster,D., Goodge,J., Silk,G., Clinical markers of serious illness in young infants: a multicentre follow-up study, Journal of Paediatrics and Child Health, 36, 221-225, 2000 **Ref Id** 140804 **Country/ies where the study was carried out** Australia **Study type** Prospective comparative cohort study **Aim of the study**	**Sample size** n= 3806 (Of which febrile: n= 313) **Characteristics** Age: Infants aged 1 to 26 weeks Gender: Not reported Ethnicity: Not reported **Inclusion criteria** - All infants aged 1 to 26 weeks presenting to the Emergency Departments of the Royal Children's Hospital, and two general	**Interventions** Occasionally drowsy Frequently drowsy Drowsy on examination Drowsy on history or examination Decreased activity Difficult breathing Moderate/severe chest wall recession Breathing difficulty on history or examination Pale on history Pallor on examination Pale on history or examination Feeding less than 50% in previous 24 hours Less than four wet nappies in 24 hours More than five vomits in 24 hours	**Details** - All infants aged 1 to 26 weeks presenting to the Emergency Departments of the Royal Children's Hospital and two general Melbourne metropolitan hospitals for the 12-month period between July 1991 and June 1992 were included in the study. - Each infant had 11 clinical markers as well as their temperature assessed, in addition to having their routine medical assessment. - Predictive values of temperature<36.4C, >38C and >38.9C were explored. - The presence of a lump was documented when a swelling >2cm was found to be present except when found at the umbilicus. - Usual Emergency Department protocols and management were carried out by the medical staff after the presence or absence of the 11 markers and temperature had been documented. - A full blood examination, blood cultures and/or urine culture was performed in all febrile infants (and chest x-	**Results** 38.1 to 38.9C Sensitivity= 17.5 (CI not reported) Specificity= 95.8 (CI not reported) PPV= 29.0 (CI not reported) NPV= 92.2 (CI not reported) Of the 313 febrile infants, 87 were sick Positive predictive values for signs/symptoms in predicting serious illness Occasionally drowsy PPV= 49.2% Frequently drowsy PPV= 76.9% Drowsy on examination PPV= 81.8%	**Limitations** No specific limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To perform a multicentre follow-up study to determine if previously identified markers of serious illness in early infancy were robust and statistically reliable **Study dates** Study date not reported, however participants included presented to the Emergency Departments during the 12 month period between July 1991 and June 1992. **Source of funding** Not reported	Melbourne metropolitan hospitals (Sunshine and District Hospital and Preston and Northcote Hospital) for the 12-month period between July 1991 and June 1992 **Exclusion criteria** Not reported	Lump>2cm	ray and faeces culture if appropriate). - Serious illness was defined as either having a serious investigation result (i.e. having a positive pathological bacterial culture from blood, urine, cerebrospinal fluid or faeces, or a chest X-ray reported as showing consolidation in a febrile patient) or by requiring significant treatment in hospital as supervised by independent hospital ward medical staff (i.e. nasogastric or i.v. fluids, parenteral antibiotics, oxygen therapy>30%, or surgery). - Comparison using positive culture alone as the end-point was explored. The diagnoses made for all seriously ill patients were documented. - The positive and negative predictive values, sensitivity and specificity were determined for each of the variables tested. The sensitivity and predictive values for each symptom and sign for infants 0-12 and 13-26 weeks of age were compared. - The clinical features of infants with diagnoses defined as being serious (e.g.: urinary tract infection or bacteremia) were explored and the number with a serious diagnosis but without clinical markers were identified.	Drowsy on history or examination PPV= 55.0% Decreased activity PPV= 83.3% Difficult breathing PPV= 24.6% Moderate/severe chest wall recession PPV= 71.4% Breathing difficulty on history or examination PPV= 32.9% Pale on history PPV= 46.7% Pallor on examination PPV= 76.2% Pale on history or examination PPV= 58.8% Feeding less than 50% in previous 24hr PPV= 63.9% Less than four wet nappies in 24hr PPV= 42.1% More than five vomits in 24hr PPV= 33.3% Lump >2cm PPV= 57.1% <u>Febrile infants who were drowsy on history or examination</u>	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Cumulative sensitivity(%): 50.6 Specificity(%): 84.1 PPV(%): 55.0 NPV(%): 81.5 <u>Febrile infants with breathing difficulty or chest wall recession</u> Cumulative sensitivity(%): 63.2 Specificity(%): 65.0 PPV(%): 41.0 NPV(%): 82.1 <u>Febrile infants who were pale on history or examination</u> Cumulative sensitivity(%): 70.1 Specificity(%): 62.8 PPV(%): 42.1 NPV(%): 84.5 <u>Febrile infants with feeding <50%</u> Cumulative sensitivity(%): 73.6 Specificity(%): 58.4 PPV(%): 40.5 NPV(%): 85.2 <u>Febrile infants with decreased activity</u> Cumulative sensitivity(%): 74.7 Specificity(%): 57.1 PPV(%): 40.1 NPV(%): 85.4 <u>Febrile infants with less than four wet nappies</u> Cumulative sensitivity(%): 77.0 Specificity(%): 57.1 PPV(%): 40.9 NPV(%): 86.6 <u>Febrile infant who is drowsy AND pale</u> PPV= 70.7%	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				No confidence intervals were reported	
Full citation Shaw,K.N., Gorelick,M., McGowan,K.L., Yakscoe,N.M., Schwartz,J.S., Prevalence of urinary tract infection in febrile young children in the emergency department, Pediatrics, 102, e16-, 1998 **Ref Id** 140950 **Country/ies where the study was carried out** USA **Study type** Cross-sectional prevalence survey **Aim of the study** Establish prevalence rates of UTI in febrile infants and young girls in an emergency department (ED) by demographics and clinical parameters. **Study dates** February 2 1995 to February 14 1996	**Sample size** n=2411 **Characteristics** Age: Infants younger than 12 months and girls younger than 2 years Gender: Male (61%) Female (39%) Ethnicity: White (12%) African-American (84%) Other (4%) **Inclusion criteria** - Temperature >/=38.3C in the ED - Boys < 1 year - Girls < 2 years - No source or minor potential source of fever as determined by examining physician (e.g.: otitis media, URI, gastroenteritis, viral exanthem)	**Interventions** General appearance Well Ill Fever >/=39C <39C Any tenderness on examination Yes No	**Details** - Urine cultures and blood cultures were obtained on the children as part of routine clinical practice in the ED. - During a 2-month pilot period, physician/physician inter-observer reliability was measured for clearly defined clinical parameters and only those items with a k statistic of >0.4 were used for a questionnaire. - This questionnaire was completed by the examining physician and nurse at the time, and a urine culture was obtained. - A team of 7 nurse researchers monitored all ED charts daily for patient eligibility, urine and blood culture results, and questionnaire completion. - Urine cultures were routinely obtained on children younger than 2 years of age by urethral catheterization by experienced ED nurses using standard sterile technique. - Urine specimens were then sent to the microbiology laboratory in sterile containers by pneumatic tube. - Urine was refrigerated, if not plated, within 10 minutes of receipt. Standard quantitative culture was performed by laboratory technologists. - A loop calibrated to deliver approximately 0.001mL was used to inoculate blood and McConkey agar plates. All plates were incubated at 35C and examined daily for growth for 2 days. - A positive result was defined as growth of a single urinary tract pathogen at >/=10^4 CFU/mL.	**Results** General appearance Well: n=1650 %prevalence(95%CI): 2.4 (1.7-3.1) P value: <0.001 Ill: n=681 %prevalence(95%CI): 5.7 (4.0-7.4) With UTI= 39/80 Without UTI= 642/2331 Fever >/=39C: n=1623 %prevalence(95%CI): 3.9 (3.0-4.8) P<0.003 With UTI= 63/80 Without UTI= 1560/2331 <39C: n=788 %prevalence(95%CI): 2.2 (1.2-3.2) Any tenderness on examination Yes: n=30 %prevalence(95%CI): 13.2 (3.7-30.7) P<0.02 With UTI= 4/80 Without UTI= 26/2331 No: n=2091 %prevalence(95%CI): 3.2 (2.4-4.0)	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding This work was supported by the Maternal and Child Health Bureau, Health Resource and Services Administration, Department of Health and Human Services.	**Exclusion criteria** - Definite source of fever [e.g.: confirmed bacterial infection (meningitis by CSF cell count, group A B-hemolytic streptococci rapid test or culture, pneumonia by chest radiograph, septic arthritis by joint aspirate) by examination (cellulitis, adenitis, osteomyelitis), specific viral infection by examination (varicella, coxsackie disease, measles), recognisable febrile disease (Kawasaki's disease)] - Current antibiotic therapy - Immunodeficiency (ANC <500) - Caretaker absent or unable to communicate		- Prevalence rates with 95%CIs were calculated for the study sample and comparison subgroups. Comparisons were made between categorical variables using x^2 test of proportions or in the case of small samples, Fisher's exact test with P</=0.05 being the priori significance level. Multiple logistic regression was used to evaluate the possibility of confounding in the relationship between race and UTI.		
Full citation Taylor,J.A., Del,Beccaro M., Done,S., Winters,W., Establishing clinically relevant standards for tachypnea in febrile children younger than 2 years, Archives of Pediatrics and Adolescent Medicine, 149, 283-287,	**Sample size** n=572 **Characteristics** <u>Age:</u> children younger than 2 years	**Interventions** Fever and Tachypnea	**Details** - From January 1992 to December 1992, respiratory rates were measured on children younger than 2 years who presented to the emergency department of Children's Hospital and Medical Center with a temperature of 38C or higher - A standardized method was used to determine respiratory rate: the examiner placed a stethoscope on	**Results** <u>Temperature => 40C</u> Pneumonia= 10/42 (23.8%) No pneumonia= 52/530 (9.8%) <u>Tachypnea</u> Pneumonia= 31/42 (73.8%) No pneumonia= 123/530 (23.2%)	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
1995 **Ref Id** 141238 **Country/ies where the study was carried out** USA **Study type** Prospective case series **Aim of the study** To determine values for defining tachypnea in febrile children younger than 2 years that best identify those at risk for pneumonia **Study dates** Not reported however respiratory rates were measured on children who presented to the emergency department between January 1992 and December 1992. **Source of funding** Not reported	Gender: not reported Ethnicity: not reported **Inclusion criteria** - Children younger than 2 years presenting to the emergency department of a children's hospital with a temperature of 38C or higher **Exclusion criteria** - Children who presented with acute wheezing and/or stridor - Children with a history of chronic pulmonary disease such as cystic fibrosis or bronchopulmonary dysplasia - If both radiologists interpreted as a chest radiograph as indeterminate, the child was excluded from the study		the patient's chest to count auscultated respirations for 60 seconds. Patient's initial temperature measured in the emergency department, the clinical diagnosis, whether a chest radiograph were ordered and whether the child was crying during the respiratory rate measurement were also recorded - For analysis, children were assigned to one of two diagnostic groups, pneumonia or no pneumonia. If a chest radiograph was not ordered and the clinical diagnosis was not pneumonia, the child was considered to have no pneumonia. If chest radiographs were obtained, they were independently classified as pneumonia, no pneumonia or indeterminate by two radiologists. If either radiologist categorized a chest radiograph as pneumonia, the patient was considered to have pneumonia, If both radiologists interpreted a radiograph as indeterminate, the child was excluded from the study - Receiver operating characteristics curves were constructed to select the values for respiratory rate that maximised sensitivity and specificity of tachypnea as a sign of pneumonia	Sensitivity, specificity, PPV and NPV of tachypnea as a sign of pneumonia Age group: 0-5 months Sensitivity% (95%CI): 83.3 (76.7-89.9) Specificity% (95%CI): 79.1 (71.9-86.3) PPV% (95%CI): 17.2 (10.5-23.9) NPV% (95%CI): 98.9 (96.0-100.0) Maximum sensitivity and specificity when tachypnea defined as a respiratory rate >59/min Age group: 6-11 months Sensitivity% (95%CI): 66.7 (60.3-73.1) Specificity% (95%CI): 79.1 (73.6-84.6) PPV% (95%CI): 16.0 (11.1-20.9) NPV% (95%CI): 97.5 (95.4-99.6) Maximum sensitivity and specificity when tachypnea defined as a respiratory rate >52/min Age group: 1-2 years Sensitivity% (95%CI): 70.8 (65.0-76.6) Specificity% (95%CI): 73.4 (67.8-79.0) PPV% (95%CI): 23.0 (17.7-28.3) NPV% (95%CI): 95.7 (94.4-97.0) Maximum sensitivity and specificity when	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				tachypnea defined as a respiratory rate >42/min All patients Sensitivity% (95%CI): 73.8 (70.2-77.4) Specificity% (95%CI): 76.8 (77.3-80.3) PPV% (95%CI): 20.1 (16.8-23.4) NPV% (95%CI): 97.4 (96.1-98.7)	
Full citation Bonadio,W.A., Smith,D.S., Sabnis,S., The clinical characteristics and infectious outcomes of febrile infants aged 8 to 12 weeks, Clinical Pediatrics, 33, 95-99, 1994 **Ref Id** 141303 **Country/ies where the study was carried out** USA **Study type** Retrospective case series **Aim of the study** To correlate the clinical characteristics and infectious outcomes of a	**Sample size** n=356 **Characteristics** Age: 8-12 weeks Gender: Not reported Ethnicity: Not reported **Inclusion criteria** - Infants aged 8 to 12 weeks with fever (rectal temperature >/=38C) presenting to the emergency department of Children's Hospital of Wisconsin **Exclusion criteria** - Infants who were culture-negative for	**Interventions** - Body temperature <40C - Body temperature >/=40C	**Details** - Subjects were infants aged 8-12 weeks with fever (rectal temperature >/=38C) presenting to the emergency department of Children's Hospital of Wisconsin, Milwaukee between January 1989 to January 1993 - Cases were identified from the daily log of ED admissions which comprises a complete record of all patients evaluated - Serious bacterial infections were defined as bacterial meningitis, bacteremia, UTI and Salmonella enteritis - The statistical analysis performed was the chi-square test to determine the significance of differences in rates of SBI as a function of two parameters-magnitude of body temperature and peripheral blood total WBC count-and to calculate predictive values of each of these parameters for outcomes of SBI.	**Results** Body temperature >/=40C With serious illness= 7/33 Without serious illness= 13/323 Sensitivity(%): 21 Specificity(%): 96 Positive predictive value(%): 35 Negative predictive value(%): 93 P value: >0.003	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
large group of febrile infants aged 8 to 12 weeks who received outpatient evaluation for sepsis, specifically distinguishing those who had serious bacterial infections from those who did not. **Study dates** Subjects presented to the emergency department between January 1989 and January 1993. **Source of funding** Not reported	bacterial pathogens and received antibiotics within 72 hours of presentation - Infants who received antipyretic medication within 4 hours of presentation				
Full citation Akpede,G.O., Sykes,R.M., Abiodun,P.O., Indications for lumbar puncture in children presenting with convulsions and fever of acute onset: experience in the Children's Emergency Room of the University of Benin Teaching Hospital, Nigeria, Annals of Tropical Paediatrics, 12, 385-389, 1992 **Ref Id** 141414 **Country/ies where the study was carried out**	**Sample size** n= 522 **Characteristics** <u>Age:</u> 1 month-6 years <u>Gender:</u> Not reported <u>Ethnicity:</u> Not reported **Inclusion criteria** - Children aged 1 month to 6 years - Rectal temperature >/=	**Interventions** Past history of convulsion Multiple seizures Focal seizures Seizure > 15 min Unrousable coma	**Details** - 522 children who presented with convulsions associated with fever at the Children's Emergency Room of the University of Benin Teaching Hospital were recruited for the study. - All children were evaluated by a detailed history and physical examination. Unrousable coma was defined as non-localizing or absent motor response to noxious stimuli. All children had an LP done irrespective of the presence/absence of features of meningeal irritation. - CSF was analysed for glucose and protein and examined for total and differential white blood cell counts and Gram stain appearance of any organisms. Samples for culture were collected into sterile bottles and inoculated onto blood, chocolate and MacConkey agar plates and incubated at 37C for 48 hours under both aerobic and anaerobic conditions.	**Results** <u>RR of past history of convulsion, multiple seizures, focal seizures, seizure > 15 min, and unrousable coma for predicting meningitis</u> <u>Past history of convulsion</u> With meningitis= 4/22 Without meningitis= 310/500 All children (including those with meningitis): Yes= 314/522 No= 208/522 Children with meningitis: Yes= 4/22 No= 18/22	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Nigeria **Study type** Prospective observational cohort **Aim of the study** To ascertain the risk factors associated with a diagnosis of bacterial meningitis and to investigate the proportion of cases which would be missed if lumbar puncture were performed only when clinical signs are present. **Study dates** 24 October 1988-23 October 1989 **Source of funding** Not reported	38C - Fever < 7 days - Convulsions associated with fever **Exclusion criteria** Not reported		- Isolates were identified by standard techniques. The diagnosis of meningitis was based on the presence of CSF pleocytosis (>5WBC/mm^3). The diagnosis of bacterial meningitis was based on the presence of a bacterial pathogen identified by Gram stain and/or culture of the CSF. - A presumed diagnosis of bacterial meningitis was made in children with no bacterial pathogen identified in the CSF but with pleocytosis and typical biochemical changes in the CSF. - The risk factors were assessed using the x^2 test. The relative risk of a child developing meningitis if the risk factor is present was calculated with 95%CI's.	RR(95%CI): 6.8 (2.3-19.8) <u>Multiple seizures</u> With meningitis= 14/22 Without meningitis= 207/500 All children (including those with meningitis): Yes= 221/522 No= 301/522 Children with meningitis: Yes= 14/22 No= 8/22 RR(95%CI): 2.4 (1.0-5.6) <u>Focal seizures</u> With meningitis= 9/22 Without meningitis= 40/500 All children (including those with meningitis): Yes= 49/522 No= 473/522 Children with meningitis: Yes= 9/22 No= 13/22 RR(95%CI): 6.7 (3.0-14.8) <u>Seizure >15mins</u> With meningitis= 6/22 Without meningitis= 174/500 All children (including those with meningitis):	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Yes= 180/522 No= 342/522 Children with meningitis: Yes= 6/22 No= 16/22 RR(95%CI): 0.7 (0.3-1.8) <u>Unrousable coma</u> With meningitis= 5/22 Without meningitis= 29/500 All children (including those with meningitis): Yes= 34/522 No= 488/522 Children with meningitis: Yes= 5/22 No= 17/22 RR(95%CI): 4.2 (1.7-10.7)	
Full citation Offringa,M., Beishuizen,A., rksen-Lubsen,G., Lubsen,J., Seizures and fever: can we rule out meningitis on clinical grounds alone?, Clinical Pediatrics, 31, 514-522, 1992 **Ref Id** 141421 **Country/ies where the study was carried out**	**Sample size** n= 309 in consecutive sample n= 92 in case: referent sample (referents were randomly selected) **Characteristics** <u>Age:</u> 3 months-6 years <u>Gender:</u> Male	**Interventions** Duration of seizure Focal seizures Focal seizures > 15 minutes Multiple seizures Drowsiness at home	**Details** - Between March 1985 and March 1987, 309 children between 3 months and 6 years with a first episode of seizure associated with fever were seen consecutively at the emergency room of two urban hospitals in the western part of the Netherlands. - Patients were identified through a review of emergency room records and a search of the hospital information system for diagnostic codes for 'seizure and fever', 'meningitis', 'encephalitis' and 'febrile seizures'. - The final diagnosis (meningitis or no meningitis), was determined for all children by review of the charts, which are standardised, problem-orientated case	**Results** <u>Focal seizure</u> Meningitis: 5/23 (22%) Non-meningitis: 9/69 (13%) Odds ratio (95% CI): 1.9 (0.6 to 6.6) Sensitivity (95% CI): 0.22 (0.08 to 0.44) Specificity (95% CI): 0.87 (0.77 to 0.94) <u>Focal seizure > 15 minutes</u> Meningitis: 10/23 (43%)	**Limitations** The physicians were aware of the lumbar puncture results when filling out some of the items regarding the physical examination. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Netherlands **Study type** Retrospective case series **Aim of the study** To determine to what extent information readily obtainable from a history and physical examination of children can serve as tools in assessing the likelihood of meningitis and to evaluate the risk factors mentioned in a previous study. **Study dates** March 1985 and March 1987 **Source of funding** Supported by a grant from the Sophia Foundation for the Sick Child and a grant from the Netherlands Health Research Promotion Programme to the Rotterdam Center for Clinical Decision Analysis.	(54%) Female (46%) Ethnicity: Not reported **Inclusion criteria** - 3 months to 6 years - First episode of seizure associated with fever **Exclusion criteria** Not reported	Vomiting at home Petechiae Nuchal rigidity (definite) Nuchal rigidity (dubious) Coma Convulsion Paresis or paralysis Suspicious physical findings Abnormal neurologic findings	records. - If a lumbar puncture had been performed, a positive culture of the CSF or a CSF-pleocytosis of at least 10 white blood cells was considered proof of meningitis. If a lumbar puncture had not been performed, the final diagnosis was based on the clinical course during subsequent observation or on re-evaluation within 24 hours in the emergency room. - Among the 309 patients with a first seizure associated with fever, 23 cases of meningitis were detected. These represent the cases in the study. From the remaining 286 children, 69 patients without meningitis were selected using a random number table to form the referent group. - The charts of the 92 patients (total) were reviewed, and data regarding preselected items of history, physical examination, and laboratory results were extracted. - The relationship between a clinical indicator and the presence of meningitis was assessed by calculating odds ratios from a 2x2 table which relates the presence or absence of the indicator to the outcome, meningitis. - Sensitivity and specificity of clinical indicators were obtained from the cases and the referents respectively; 95%CI for these sensitivities and specificities were calculated using the exact method. - The probability of meningitis given the presence or absence of a clinical indicator was assessed through calculation of likelihood ratios for the presence and absence of that indicator and their 95%CIs.	Non-meningitis: 5/69 (7%) Odds ratio (95% CI): 9.8 (2.8 to 33.6) Multiple seizures Meningitis: 10/23 (43%) Non-meningitis: 15/69 (22%) Odds ratio (95% CI): 2.8 (1.0 to 7.6) Either a focal seizure or multiple seizures Meningitis: 17/23 (74%) Non-meningitis 26/69 (38%) Odds ratio (95% CI): 4.6 (1.6 to 13.4) LR- 0.42 (95% CI 0.21 to 0.85) LR+ 1.9 (95% CI 1.33 to 2.89) PPT+ 13% (9 to 18%) PPT- 3% (2 to 6%) Drowsiness at home Meningitis: 7/23 (30%) Non-meningitis: 4/69 (6%) Odds ratio (95%CI): 7.1 (1.9 to 27.3) Vomiting at home Meningitis: 11/23 (48%) Non-meningitis: 13/69 (19%) Odds ratio (95%CI): 3.9 (1.4 to 10.9)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Petechiae Meningitis: 3/23 (13%) Non-meningitis: 0/69 (0%) Odds ratio (95% CI): 23.7 (1.2 to 478)* Nuchal rigidity (definite) Meningitis: 11/23 (48%) Non-meningitis: 0/69 (0%) Odds ratio (95% CI): 128 (7.1 to 2311)* Nuchal rigidity (dubious) Meningitis: 2/23 (9%) Non-meningitis: 6/69 (9%) Odds ratio (95% CI): 2.1 (0.4 to 11.9) Coma Meningitis: 6/23 (26%) Non-meningitis: 0/69 (0%) Odds ratio (95% CI): 52 (2.7 to 960)* At least one of petechiae, nuchal rigidity (definite), or coma Meningitis: 16/23 (70%) Non-meningitis: 0/69 (0%) Odds ratio (95% CI): 305 (17 to 2,500)* LR- 0.30 (95% CI 0.16 to 0.57) LR+ infinite (95% CI 6.0 to infinite)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				PPT+ 100% (31 to 100%) PPT- 2% (1 to 4%) <u>Either a focal seizure or multiple seizures, or one of petechiae, nuchal rigidity (definite), or coma</u> Meningitis: 23/23 (100%) Non-meningitis: 45/69 (65%) Odds ratio not reported LR- 0 (95% CI 0 to 1.0) LR+ 1.53 (95% CI 1.29 to 1.82) PPT+ 10% (9 to 12%) PPT- 0% (0 to 7%) <u>Nuchal rigidity (dubious)</u> Meningitis: 2/23 (9%) Non-meningitis: 6/69 (9%) Odds ratio (95% CI): 2.1 (0.4 to 11.9) <u>Drowsiness</u> Meningitis: 12/23 (52%) Non-meningitis: 18/69 (26%) Odds ratio (95% CI): 6.8 (2.1 to 22.0) (excluding children with coma) <u>Convulsion on examination</u> Meningitis: 7/23 (30%) Non-meningitis: 6/69 (9%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Odds ratio (95%CI): 4.6 (1.4 to 14.6) <u>Paresis or paralysis on examination</u> Meningitis: 7/23 (30%) Non-meningitis: 6/69 (9%) Odds ratio (95% CI): 4.6 (1.4 to 14.6) <u>At least one of nuchal rigidity (dubious), drowsiness, convulsing on examination, paresis or paralysis on examination</u> Meningitis: 21/23 (91%) Non-meningitis: 24/69 (35%) Odds ratio (95% CI): 19.7 (4.3 to 91.1) After exclusion of children with petechiae, nuchal rigidity (definite), or coma: Meningitis: 5/7 (71%) Non-meningitis: 24/69 (35%) Odds ratio not reported LR- 0.44 (95% CI 0.13 to 1.43) LR+ 2.05 (95% CI 1.16 to 3.63) PPT+ 13% (8 to 21%) PPT- 3% (1 to 14%) <u>Suspicious physical findings</u> Raw data not reported Sensitivity (95% CI): 0.13 (0.03 to 0.34) Specificity (95% CI): 1.00 (0.96 to 1.00) <u>Abnormal neurologic findings</u>	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Raw data not reported Sensitivity (95% CI): 0.65 (0.43 to 0.84) Specificity (95% CI): 0.91 (0.82 to 0.97) * Odds ratio and 95%CI determined after adding a value of 0.5 in each cell of tables containing a zero count.	
Full citation Baskin,M.N., O'Rourke,E.J., Fleisher,G.R., Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone, Journal of Pediatrics, 120, 22-27, 1992 **Ref Id** 141480 **Country/ies where the study was carried out** USA **Study type** Prospective consecutive cohort study **Aim of the study** To determine the outcome of outpatient treatment of febrile infants 28 to 89 days of age with intramuscular	**Sample size** n=503 **Characteristics** Age: 28-89 days Gender: Not reported Ethnicity: Not reported **Inclusion criteria** - Age>/=28 days and <90 days - Temperature >/=38C, obtained rectally in the emergency department, or a parental history of an equivalent rectal temperature - No ear, soft tissue, joint, or bone infection identified on physical	**Interventions** AIOS score Temperature	**Details** - Comprehensive history, physical examination and laboratory evaluation were obtained for each patient. Historical factors including gestational age, any perinatal complications and any previous antimicrobial therapy, were documented. - For all patients, an attending physician scored the infant's general appearance by using the Acute Illness Observation Scale (AIOS). - After the clinical and laboratory evaluations were completed, the infants received an intramuscular injection of 50mg/kg ceftriaxone and were sent home. - The follow-up protocol included 3 telephone calls and one return visit to the ED. The first telephone interview was done 12 hours after entry into the study. The infants were then re-examined in the ED 24 hours after entry into the study and received a second dose of ceftriaxone at that time. - The parents received additional follow-up telephone calls both 48 hours and 7 days after the patient's entry into the study. When culture results became available, patients with bacterial growth in cultures of blood, CSF urine, or stool were immediately recalled to the ED for appropriate antimicrobial therapy. The patient's chart was reviewed 3 months to 1 year after enrolment in the study.	**Results** P values between those with (Group 1: n = 27)and without a bacterial source of infection (Group 2: n = 476) Temperature Group 1: 39.0±0.6^{o}C Group 2: 38.9±0.6^{o}C P = 0.01 Acute Illness Observation Scale Score (6-30) Group 1: 8.0±3.2 Group 2: 7.3±2.2 P = NS Of those with a bacterial source of infection: Occult bacteremia= 8 UTI with bacteremia= 1 UTI without bacteremia= 8 Bacterial gastroenteritis without bacteremia= 10	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
administration of ceftriaxone. **Study dates** February 3, 1987-April 30 1990 **Source of funding** Not reported	examination - No source of infection identified on initial screening laboratory tests: a) Cerebrospinal fluid leukocyte count <10 x 10^6 cells/L b) Urinalysis demonstrating <10 leukocytes per high-power field (if microscopic examination performed) or results of dipstick test negative for leukocyte esterase activity c) No infiltrate on chest radiograph, if obtained - Peripheral leukocyte count <20 x 10^9 cells/L - Judged not to require admission to the hospital for any reason other than parenteral administration of antimicrobial agents (vital signs in the normal range for age and temperature, not ill appearing, not dehydrated, taking fluids, and having cooperative and reliable parents) - Care giver available by		- SBI was defined as bacterial growth in cultures from blood, CSF, urine or stool. A UTI was defined by a urine culture with >1000 colonies/ml of a single organism in urine obtained by bladder catheterization. - Data were analysed using the two-tailed Student t test for continuous numeric normally distributed values and the Wilcoxon rank sum test for values not distributed normally. The chi-square technique was used for categorical variables, with the Yates correction for all 2x2 tables. When the expected number of individuals in any cell was less than five, a Fisher Exact Test was used.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	telephone - No antimicrobial agents received within the preceding 48 hours - No allergies to B-lactam antimicrobial agents - No immunization with diphtheria and tetanus toxoids and pertussis vaccine within 48 hours **Exclusion criteria** Not reported				
Full citation Baker,M.D., Avner,J.R., Bell,L.M., Failure of infant observation scales in detecting serious illness in febrile, 4- to 8-week-old infants, Pediatrics, 85, 1040-1043, 1990 **Ref Id** 141584 **Country/ies where the study was carried out** USA **Study type** Diagnostic accuracy study	**Sample size** n=126 **Characteristics** Age: 29-56 days Gender: Male (53%) Female (47%) Ethnicity: Black (67%) White (33%) **Inclusion criteria** - Infants aged 29-56 days with rectal temperatures in excess	**Interventions** Yale observation score - Quality of cry - Reaction to parent stimulation - State variation - Colour - Hydration - Response (talk, smile) to social overtures	**Details** - Each infant was scored (1 to 5) on each of six items by an Emergency Department attending physician before history and physical examination. To minimize interobserver variation, only four Emergency Department attending physicians experienced in the use of the scale participated in the completion of the initial observation score. - History was then taken and physical examination performed by the managing resident and a complete sepsis workup (complete blood count, urinalysis, lumbar puncture, chest roentgenograms, blood culture, urine culture, CSF culture) was obtained. Other laboratory tests were performed as required. - The diagnosis of a UTI was made by the isolation of at least 10^3 colonies of a single organism on a catheterized or suprapubic urine specimen. - Aseptic meningitis was defined as a CSF pleocytosis (white blood cells >10/mm^3 and red blood cells	**Results** 37 children had serious illness, 89 children did not have serious illness 12 children had bacterial disease, 114 children did not have bacterial disease Predictive value of observation score: serious illness Observation score >10 (ill): serious illness present: 17/37 serious illness absent: 18/89 Observation score </=10 (well): serious illness present: 20/37 serious illness absent: 71/89 Sensitivity (%): 46 Specificity (%): 80 PPV (%): 49	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To determine the usefulness of this observation scale for identifying serious illness in febrile, 4-8 week-old infants. **Study dates** July 1 1987-July 15 1988 **Source of funding** Not reported	of 38.2C presenting to The Children's Hospital of Philadelphia Emergency Department. **Exclusion criteria** Not reported		<100/mm^3) with sterile blood and CSF cultures. - The diagnosis of pneumonia was based on an infiltrate on a chest roentgenogram. - Bronchiolitis was diagnosed by tachypnea or wheezing supported by a chest roentgenogram. - Serious illness was defined in the following ways: isolation of bacterial pathogens on cultures of blood, CSF, urine, stool or joint fluid; pneumonia; or aseptic meningitis.	NPV (%): 78 <u>Predictive value of observation score: bacterial disease</u> Observation score >10 (ill): bacterial disease present: 4/12 bacterial disease absent: 31/114 Observation score </=10 (well): bacterial disease present: 8/12 bacterial disease absent: 83/114 Sensitivity (%): 33 Specificity (%): 73 PPV (%): 11 NPV (%): 91 Breakdowns of score by diagnosis are also reported in the paper	
Full citation Baker,R.C., Seguin,J.H., Leslie,N., Gilchrist,M.J., Myers,M.G., Fever and petechiae in children, Pediatrics, 84, 1051-1055, 1989 **Ref Id** 141625 **Country/ies where the study was carried out** USA **Study type** Prospective observational	**Sample size** n=190 **Characteristics** <u>Age:</u> Age range was from 3 months to 15 years, with 54% of the patients younger than 24 months of age <u>Gender:</u> Male (61%) Female (39%) <u>Ethnicity:</u> Racial distribution reflected that of the referral area (181	**Interventions** Ill appearance Signs of meningeal irritation	**Details** - Subjects were recruited from the Cincinnati Children's Hospital Medical Center between November 1, 1982 and October 31, 1983 - The number of petechiae were estimated using a scale of 0 to 2 e.g., 0 indicated <10 petechiae and 2 indicated generalized petechiae. The locations of petechiae were classified as: above the nipple line including the head and upper extremities, the trunk below the nipple line, and the lower extremities. - Various laboratory evaluations were carried out. Meningococcal disease was diagnosed by detection of N meningitidis on blood or cerebrospinal fluid culture. - The two-tailed student t-test and Fisher's exact test were used to compare the historical, physical and laboratory parameters of patients with documented	**Results** 15 children had documented invasive bacterial infection 39 children had non-bacteremic causes of infection (inc. 20 children with bacterial infection - 19 with S pyogenes pharyngitis and 1 with Escherichia coli) 28 children had a viral cause 136 children had no etiological agent identified <u>P value comparing ill appearance and signs of meningeal irritation in those with and without invasive bacterial disease</u>	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
cohort study **Aim of the study** To determine the incidence of meningococcal disease in children with fever and petechiae , the clinical predictors of meningococcal disease and the appropriate initial treatment of children with these clinical findings. **Study dates** November 1, 1982 to October 31, 1983 **Source of funding** Not reported	white, 9 black) **Inclusion criteria** - The presence of a fever or history of fever (>38C) - A petechial rash detected before venipuncture or lumbar puncture - Age less than 21 years **Exclusion criteria** - Children with purpura fulminans, known bleeding diatheses and neonates		invasive bacterial infection (group I) and those with documented non-bacteremic infection (group II). Sensitivity, specificity and positive predictive values were calculated.	Ill appearance: With invasive disease= 7/15 (47%) Without invasive disease= 4/39 (10%) P=0.003 Signs of meningeal irritation: With invasive disease= 5/15 (33%) Without invasive disease= 1/39 (3%) P=0.004 Generalised petechiae: With invasive disease=6/15 (40%) Without invasive disease= 5/45 (11%) P=0.004	
Full citation Crocker,P.J., Quick,G., McCombs,W., Occult bacteremia in the emergency department: diagnostic criteria for the young febrile child, Annals of Emergency Medicine, 14, 1172-1177, 1985 **Ref Id** 141826 **Country/ies where the study was carried out**	**Sample size** n=201 **Characteristics** Age: 6 months - 2 years Gender: Male (48%) Female (52%) Ethnicity: Caucasian (45%) Black (28%) Hispanic (22%) Asian	**Interventions** Temperature Irritability Lethargy	**Details** - Data were collected from the ED of Darnall Army Community Hospital, Fort Hood, Texas, and Scott and White Hospital, Temple, Texas between October 1982 and January 1984. - All parents of studied infants gave written informed consent using a standard disclosure form prior to inclusion in the study. - A CBC, an erythrocyte sedimentation rate, a single aerobic blood culture and a two-view chest radiograph were obtained on all patients. - Blood cultures were reviewed daily for 5 days and at ten days to identify positive cultures. All laboratory	**Results** P value comparing temperature, irritability, and lethargy in bacteremic and non-bacteremic patients Temperature (C) Bacteremic patients: 40.0+/-0.43 Non-bacteremic patients: 40.1+/-0.27 P value: NS Irritability	**Limitations** It is not clear whether the results of the reference tests were read without knowledge of the demographic data. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
USA **Study type** Prospective study **Aim of the study** To identify specific prospective diagnostic criteria for 'occult bacteremia'. **Study dates** October 1982-January 1984 **Source of funding** Not reported	(3%) Other (2%) [Ethnicity percentages estimated from graph] **Inclusion criteria** 6 months to 2 years Rectal temperature >/= 39.4C No viral illness **Exclusion criteria** Infants with fever less than 39.4C, vomiting and diarrhoea, croup, or viral exanthem or enanthem.		results and patient records were reviewed at least ten days after initial presentation in order to identify any patient morbidity and to ensure that adequate follow-up had been completed. - Any patient with positive blood culture was called back to the ED and referred to the Pediatric Department for management. - Biographical and historical data were collected on standard forms and correlated by the Department of Biostatistics at Scott and White Hospital. - Student's t test was used to determine the statistical significance of differences between groups of numeric data, and a chi-square test was used to evaluate the non-numeric data. Multivariate linear regression analysis was used in attempting to construct a complex model predictive of bacteremia. The P value was significant at P</=0.05.	Bacteremic patients: 18/28 Non-bacteremic patients: 78/173 P value: NS Lethargy Bacteremic patients: 4/28 Non-bacteremic patients: 38/173 P-value: NS	
Full citation McCarthy,P.L., Lembo,R.M., Baron,M.A., Fink,H.D., Cicchetti,D.V., Predictive value of abnormal physical examination findings in ill-appearing and well-appearing febrile children, Pediatrics, 76, 167-171, 1985 **Ref Id** 141840	**Sample size** n=103 **Characteristics** Age: </=24 months Gender: Not reported Ethnicity: Not reported	**Interventions** Yale Observation Scale-Quality of cry, Reaction to parent stimulation, State variation, Colour, Hydration, Response (talk, smile) to social overtures Physical examination findings	**Details** - Infants aged 24 months or younger with temperature >/=38.3C coming to a Primary Care Center-Emergency Room from July 1 1982 to November 24 1982 were enrolled in the study. - Children were initially observed by an attending physician and classified as to whether they appeared ill or well. A history was then taken by a resident paediatrician who served as the prime questioner and two attending physicians A and B. - The physical examination was performed by attending physician B and the paediatric resident independently; as history and physical examination findings were	**Results** Frequency of physical examination findings suggesting serious illness in ill-appearing and well-appearing children Ill appearance Serious illness= 14/26 No serious illness= 8/77 - Of 22 ill-appearing children, 14 (64%) had physical examination findings suggestive of	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA **Study type** Prospective observational study **Aim of the study** To investigate the interaction between a febrile child's appearance, history and physical examination findings and the presence of serious illness by asking the following questions: 1) Do ill-appearing febrile children more frequently have history and physical examination findings that suggest a serious illness than well-appearing children? 2) Do ill-appearing febrile children with abnormal history and physical examination findings more often have a serious illness as defined by a positive laboratory test than well-appearing febrile children with abnormal findings? **Study dates**	**Inclusion criteria** Children aged </=24 months with fever >/=38.3C **Exclusion criteria** Not reported	Buccal induration (Bloody) diarrhoea Erythema Full fontanel Grunt Mottled/gray colour Nuchal rigidity Rales Retractions Rhonchi Swelling Tachypnea	elicited, they were noted by attending physician A on a blank lined form and scored as to whether they did or did not suggest a serious illness. If disagreements arose, the child was re-examined simultaneously by the two physicians and only those findings which these physicians agreed were present were considered present. - The Yale Observation Scales were used to judge whether a child appeared ill or well. A Yale Observation Score of greater than 10 defined a child as appearing ill. - After the observation, history and physical examination, the resident made the decision about performing laboratory studies. - A serious illness was defined as an illness associated with one or more of the following abnormal laboratory results: 1) a bacterial pathogen isolated from the CSF, blood, urine, stool, deep soft tissue, or pleura 2) an infiltrate seen on chest roentgenogram, aseptic CSF pleocytosis, or abnormal serum electrolyte values such as hypernatremia or acidosis 3) hypoxemia during a lower respiratory tract infection. - Children were followed by the appropriate attending physician or resident until the illness resolved and study patient charts were reviewed 1 to 6 months after the visit in order to monitor the occurrence of serious illness in patients. - The difference in the frequency of patients with history or physical examination findings suggesting serious illness among ill-appearing versus well-appearing febrile children and the difference in the frequency of patients with laboratory-documented serious illnesses among ill-appearing febrile children with abnormal clinical findings, versus well-appearing febrile children with abnormal clinical findings were studied using Fisher's exact test.	a serious illness - Of 81 well-appearing children, 12 (15%) had physical examination findings suggestive of a serious illness - These differences are significant P<0.001 by Fisher's exact test <u>PPV of physical examination findings that suggest serious illness among ill-appearing and well-appearing children</u> <u>Ill-appearing children</u> PPV: 79% <u>Well-appearing children</u> PPV: 25%	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
July 1982 to November 1982 **Source of funding** This work was supported in part, by a General Pediatric Academic Development Award from the Robert Wood Johnson Foundation					
Full citation Van,Nguyen Q., Nguyen,E.A., Weiner,L.B., Incidence of invasive bacterial disease in children with fever and petechiae, Pediatrics, 74, 77-80, 1984 **Ref Id** 141897 **Country/ies where the study was carried out** USA **Study type** Retrospective chart review **Aim of the study** To determine the incidence of bacterial sepsis in the genesis of fever and petechiae and to identify factors that might enable the physician to distinguish patients with fever and	**Sample size** n=129 **Characteristics** Age: 1 month-16.5 years Gender: Male (61%) Female (39%) Ethnicity: White (93%) Black (5.4%) Hispanic (1.6%) **Inclusion criteria** Children 1 month to 16.5 years (mean 33.9 months) with fever and petechiae. **Exclusion criteria** Patients with more than just fever and petechiae i.e. those with fever, petechiae and shock;	**Interventions** Mean temperature Fever > 40C	**Details** - The charts of all patients admitted for evaluation of fever and petechiae during a 5 year period were reviewed. - These patients had been admitted to the paediatric services of the Upstate Medical Center from January 1978 through December 1982. - Charts were reviewed for final etiologic diagnosis, demographic data, temperature, location of petechiae, and routine laboratory results such as WBC count, and differential and CSF analysis.	**Results** P value comparing mean temperature in children with and without serious bacterial infection Group 1 (n = 26)mean +/- SD: 39.9+/-0.96 Group 2 (n = 103)mean +/- SD: 39.1+/-3.9 p>0.2 Sensitivity and specificity of fever > 40C for predicting serious bacterial infection With invasive bacterial disease: 17/26 Without invasive bacterial disease: 62/103 Sensitivity(%): 65.4 Specificity(%): 60.2 Invasive bacterial disease were: Neisseria meningitidis meningitis and/or sepsis= 13 Haemophilus influenzae type b meningitis	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
petechiae caused by bacterial sepsis from those without such an etiology. **Study dates** January 1978-December 1982 **Source of funding** Not reported	fever and purpura; and purpura fulminans were excluded from analysis.			and/or sepsis= 8 Streptococcus pneumoniae meningitis and sepsis= 1 Staphylococcus aureus sepsis and osteomyelitis= 1 S aureus endocarditis= 1 Escherichia coli urinary tract infection= 2 Invasive bacterial disease were: Presumed viral syndrome= 59 Aseptic meningitis= 10 Enterovirus infection= 4 Adenovirus infection= 1 Herpangina= 1 Streptococcal pharyngitis= 3 Scarlet fever= 1 Otitis media= 5 Pneumonia= 2 Mycoplasma pneumoniae pneumonia= 1 Roseola= 1 Kawasaki syndrome= 1 Henoch-Schoenlein purpura= 1 Idiopathic thrombocytopenic purpura= 1 Febrile convulsions= 5 MMR immunisation reaction= 1 Presumed ampicillin rash= 1 Fever and neutropenia/acute myelogenous leukemia= 1 Fever of unknown cause= 4	
Full citation Joffe,A., McCormick,M., DeAngelis,C., Which children with febrile seizures need lumbar puncture? A decision analysis approach, American Journal of Diseases of Children, 137, 1153-1156, 1983	**Sample size** n=241 **Characteristics** Age: 6 months-6 years Gender: Not reported	**Interventions** Seizure in emergency room Focal seizure Suspicious physical findings Abnormal neurological	**Details** - In both settings, study patients were identified through a review of emergency room record files and at John Hopkins Hospital, a search of computerised records. - The charts of all patients were reviewed by one of the authors and data regarding 12 preselected items of history and physical examinations as well as laboratory test results were extracted. - The 12 items included history of fever at home, health	**Results** Sensitivity, specificity, PPV and NPV for seizure in emergency room, focal seizure, suspicious physical findings, and abnormal neurological findings for predicting meningitis (alone and in combination) Seizure in emergency room Sensitivity: 0.23 Specificity: 0.96 PPV: 0.27	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 141925 **Country/ies where the study was carried out** USA **Study type** Retrospective diagnostic accuracy study **Aim of the study** To identify factors that can be obtained from the history and physical examination that could serve as a screening test for the presence of meningitis to guide in selection of patients warranting LP. **Study dates** Jan 1 1978 to Dec 31 1980 **Source of funding** Grant from the Robert Wood Johnson Foundation Program in General Pediatric Academic Development.	Ethnicity: Not reported **Inclusion criteria** - Children aged 6 months to 6 years who were brought to the emergency room of either Sinai Hospital or Johns Hopkins Hospital in Baltimore with a first episode of seizure and fever in a 36-month period (Jan 1 1978-Dec 31 1980) **Exclusion criteria** - Children who did not undergo LP were eliminated from the study unless telephone follow-up or chart review documented the outcome of the acute illness; those with a predisposition to meningitis (e.g.: the presence of a CNS shunt) were also excluded.	findings	history for 48 hours prior to the seizure, care sought within 48 hours prior to the seizure, a family history of seizures, the duration of the seizure, the type of seizure, appearance at time of visit, the level of consciousness, the behaviour of the child as observed by the examiner, the degree of irritability, suspicious physical and neurologic findings. - Patients were categorized into 2 groups: those with normal CSF findings who were sent home and those with CSF pleocytosis who were hospitalized. - The proportion of children in each group with the presence of each of the historical and physical items were compared by x^2 analysis. For any item shown to discriminate at the P<0.05 level between patients with and without meningitis, its sensitivity, specificity, PPV and NPV as a screening test for meningitis were calculated.	NPV: 0.95 Focal seizure Sensitivity: 0.38 Specificity: 0.91 PPV: 0.20 NPV: 0.96 Suspicious physical findings Sensitivity: 0.23 Specificity: 0.97 PPV: 0.23 NPV: 0.96 Abnormal neurologic findings Sensitivity: 0.92 Specificity: 0.84 PPV: 0.26 NPV: 0.99 Focal seizure or suspicious physical findings Sensitivity: 0.46 Specificity: 0.89 PPV: 0.20 NPV: 0.97 Focal seizure or abnormal neurologic findings Sensitivity: 0.92 Specificity: 0.82 PPV: 0.24 NPV: 0.99	
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
McCarthy,P.L.,			- From November 1, 1980 to March 1, 1981,	Diagnostic accuracy of a model consisting	No serious

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Sharpe,M.R., Spiesel,S.Z., Dolan,T.F., Forsyth,B.W., DeWitt,T.G., Fink,H.D., Baron,M.A., Cicchetti,D.V., Observation scales to identify serious illness in febrile children, Pediatrics, 70, 802-809, 1982 **Ref Id** 141976 **Country/ies where the study was carried out** USA **Study type** Diagnostic acccuracy study **Aim of the study** To identify those observation items that could be used to identify, reliably and validly, serious illnesses in children with fever **Study dates** November 1 1980 to March 1 1981 **Source of funding** None reported	n=312 **Characteristics** Age: </=24 months Gender: Not reported Ethnicity: Not reported **Inclusion criteria** Children aged </=24 months with fever >/= 38.3C(101.0F) seen at the Yale-New Haven Hospital Primary Care Center Emergency Room **Exclusion criteria** Not reported	1 Quality of cry 2 Reaction to parents 3 State variation 4 Colour 5 State of hydration 6 Response to social overtures 7 Playing with object 8 Movement 9 Respirations 10 Appearance of eyes 11 Response to visual stimulation	consecutive children aged </=24 months with fever >/=38.3C(101.0F) were evaluated - The patients were seen in the Yale-New Haven Hospital Primary Care Center-Emergency Room (PCC) or in one private practice in Milford, CT - In the PCC, the child was observed by one or two attending physicians, a resident, and a nurse prior to history and physical examination and before antipyretics were given - The same two attending physicians saw one third of the patients in the PCC in order to evaluate interobserver reliability. In the private practice, the patients were seen by a single observer. - A previous report disclosed that all of the data describing seriously ill children or impairment could be categorised into one of 14 areas: colour, hydration, respirations, movement, eye appearance, quality of cry, reaction to parents' stimulation, reaction to observer's stimulation, state variation, response to noise, response to visual stimulation, response to social overtures, reaching or grasping for a presented object, and playing with a presented object. The observation data identified in the review were next used to construct scale points for these 14 areas. - Each area was initially given a three-point scale (normal, moderate, severe) and was then developed into a five-point scale in order to indicate impairment somewhere between normal and moderate or between moderate and severe. - The 14 items were scored on consecutive febrile children without any communication between observers. Oral consent was obtained from the parent. - Items that required minimal or no observer interaction with the child were scored first (colour, hydration,	of signs/symptoms 1 to 6 for predicting serious illness Sensitivity: 77% Specificity: 88% PPV: 56% NPV: 4.7% Height of fever did not add to these values Diagnostic accuracy of a model consisting of signs/symptoms 1 to 11 for predicting serious illness Sensitivity: 65% Specificity: 90% 'Predictive value' (the authors did not specify if this was positive or negative): 55% Not a significant improvement over the 6 item model above Results of the predictive model A patient score was derived by summing the scores of the individual items Score of =< 10: Serious illness= 3/36	limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			respirations, movement and appearance of eyes). Items that required interaction with the child were then scored (quality of cry, reaction to parent stimulation, reaction to observer stimulation, state variation, response to visual stimulation, response to noise stimulation, response to social overtures, reaching or grasping for a presented object and playing with a presented object). - After observation, history and physical examination were performed by the resident and laboratory studies ordered at his or her discretion. The child was then admitted to the hospital or sent home with follow-up. - Results of laboratory studies and the clinical course were reviewed by one of the physicians within a week of the visit - Two months after completion of the study, the hospital PCC charts of all patients were reviewed to identify any additional laboratory or follow-up clinical information related to the acute febrile episode. - If patients in the study did go to the other facility during their illness, the researchers were made aware of the results of that evaluation - Serious illness was defined in the following ways: 1) bacterial pathogens were isolated on cultures of blood, CSF, urine, stool, joint fluid, or deep soft tissue aspirates 2) abnormalities of electrolytes (hypernatremia, acidosis), chest roentgenograms (infiltrates), blood gases (hypoxia in bronchiolitis), or CSF(pleocytosis) were documented 3) Patients who did not meet criteria 1 or 2 but who, because of bronchiolitis, required prolonged hospitalization, intravenous hydration and pulmonary toilet - Stepwise multiple regression analysis was conducted to identify observation items predictive of serious illness. Sensitivity, specificity and PPV of the model for	No serious illness= 162/194 Score of 11 to 15: Serious illness= 11/36 No serious illness= 31/194 Score of => 16: Serious illness= 12/36 No serious illness= 1/194 None of the individual 11 signs/symptoms performed as well as the predictive model. <u>Specific sign/symptoms</u> Appearance of eyes (moderate or severe impairment): Sensitivity: 85% Specificity: 50% Positive predictive value: 24% Response to social overtures (moderate or	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			predicting serious illness were calculated. -The six-item predictive model was then validated against the original sample of 165 children, which was divided into two groups using a random number table	severe impairment): Sensitivity: 85% Specificity: 50% Positive predictive value: 24% <u>Validation of the six item model</u> Group A: Sensitivity: 83% Specificity: 83% PPV: 48% Group B: Sensitivity: 64% Specificity: 88% PPV: 50% These compare with the values for the predictive model from the full sample	
Full citation Crain,E.F., Shelov,S.P., Febrile infants: predictors of bacteremia, Journal of Pediatrics, 101, 686-689, 1982	**Sample size** n=175 **Characteristics**	**Interventions** - Tone - Activity level during examination	**Details** - The study was performed at the Bronx Municipal Hospital Center. Subjects who were 8 weeks or younger presented to the paediatric emergency room between October 1, 1979 and September 30, 1981 with	**Results** Not significantly associated with bacteremia: -temperature >/=38.6C(the median)	**Limitations** No serious limitations **Other**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 141977 **Country/ies where the study was carried out** USA **Study type** Prospective observational study **Aim of the study** To gain information on the incidence of bacteremia in a group of young infants with fever who presented to the emergency room and to determine if there were any criteria by which house officers at the time of the first examination could predict which infants would turn out to have bacteremia **Study dates** Not reported however infants presented to the paediatric emergency room between October 1, 1979 and September 30, 1981. **Source of funding** Not reported	Age: </= 8 weeks Gender: Not reported Ethnicity: Not reported **Inclusion criteria** - Rectal temperature >/= 38C (100.4F) - </= 8 weeks of age presenting to the paediatric emergency room of the Bronx Municipal Hospital Center between October 1, 1979 and September 30, 1981 **Exclusion criteria** Not reported	- Cry - Irritability - Impression of sepsis - Temperature >/=38.6C(the median)	a rectal temperature >/=38C. - All infants received a full evaluation for sepsis and were admitted for antibiotic therapy pending culture results. - Each infant was examined by a paediatric house officer who took a complete history, performed a physical examination and recorded his or her impressions of the infant on a number of items including tone, colour, activity, cry and irritability. An overall impression of the likelihood that the infant had sepsis was also recorded using a 3-point scale. - An evaluation for sepsis was then performed including a complete blood count, blood cultures, serum glucose concentration, lumbar puncture for cell count, chemical analysis and culture and urinalysis and urine culture	-impression of irritability -tone -cry -activity level during the examination (p value not given) Significantly associated with bacteremia: - Impression of sepsis (strong or ambivalent) With bacteremia= 5/5 Without bacteremia= 54/129 p < 0.02	**information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation McCarthy,P.L., Jekel,J.F., Stashwick,C.A., Spiesel,S.Z., Dolan,T.F., Sharpe,M.R., Forsyth,B.W., Baron,M.A., Fink,H.D., Rosenbloom,M.L., Etkin,T., Zelson,J.H., Further definition of history and observation variables in assessing febrile children, Pediatrics, 67, 687-693, 1981 **Ref Id** 142022 **Country/ies where the study was carried out** USA **Study type** Correlation analysis and a diagnostic accuracy study **Aim of the study** To define more precisely the variables on which overall assessment (clinician judgment) is based and to study the relationship between scoring for these variables and serious illness. **Study dates**	**Sample size** n=262 **Characteristics** Age: </=24 months Gender: Not reported Ethnicity: Not reported **Inclusion criteria** =< 24 months Fever => 38.3C **Exclusion criteria** Not reported	**Interventions** Unnamed (basis of McCarthy scale)	**Details** - Children were seen in two locations: the Primary Care Center of Yale-New Haven Hospital, which includes the paediatric emergency room and the general paediatric clinic, and in four offices of paediatricians engaged in private practice in New Haven. - In the Primary Care Center, each child was seen by two or three observers prior to antipyresis or a physical examination. One observer was attending paediatrician, the second observer was almost always the paediatric house officer caring for the patient, and the third observer was the charge nurse in the general clinic or the emergency room. In the private office setting, the child was evaluated by the paediatrician alone prior to physical examination. - Each observer was given a blank, lined form with an opportunity to list history and observation variables thought to be important by that observer in arriving at a judgment of degree of illness (overall assessment). - After recording the nature of the variable, each observer scored the individual variable on a four-point scale: normal=1; mildly impaired=2; moderately impaired=3; severely impaired=4. The same scale was used to score overall assessment. - The sequence of evaluation was as follows: the history was taken by the house officer, and the one or two other observers could ask additional historic questions simultaneously. History variables were listed and scored by each observer at this time. Then all observers observed the child prior to the physical examination and listed and scored observation variables each thought was most important in arriving at a judgment of degree of illness. An overall assessment was then scored. - No discussion of the patient took place among	**Results** Sensitivity, specificity, and predictive value for overall assessment score of 3 or 4 for serious illness for different observers Observer: Attending paediatrician Sensitivity(%): 70.6 Specificity(%): 79.3 Predictive value (%): 28.6 Observer: House officer Sensitivity(%): 64.7 Specificity(%): 78.9 Predictive value (%): 26.8 Observer: Nurse Sensitivity(%): 54.6 Specificity(%): 89.1 Predictive value (%): 37.5	**Limitations** Private paediatricians did not have their observations checked by other observers **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
July 27 1979-Jan 31 1980 **Source of funding** The study was supported in part by a General Academic Pediatric Development Award from the Robert Wood Johnson Foundation.			observers. There was no limit to the number of history or observation items which could be listed and scored. - A similar sequence of evaluation, but without multiple observers was carried out by the private paediatricians. - The child was then examined by the house officer (or the private paediatrician) and laboratory studies ordered based on his/her judgment. Clinical follow-up was provided by the house officer if the child was not admitted to the hospital. - The relationship of different history and observation variables to overall assessment and to the final diagnosis was analysed both for the individual variables and also for categories of variables which could be readily formed from grouping individual variables. - The Pearson correlation coefficient was used to determine the relation between scoring for variables and scoring for degree of illness. A Mann-Whitney U test was used to compare the means +/-SD of scores for individual variables in children with serious illnesses and those without serious illnesses. - A serious illness was defined as an illness associated with an abnormal result from one of the following laboratory tests: lumbar puncture, chest roentgenogram; blood urine, or stool culture or serum electrolytes. - The relation between selected mean scores for overall assessment and patients with positive tests was studied by utilization of sensitivity, specificity and predictive value.		
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
McCarthy,P.L., Jekel,J.F., Stashwick,C.A., Spiesel,S.Z., Dolan,T.F.,Jr., History and observation	n=219	Scoring system based on:	- From August 1 1977 to February 1 1978, the faculty attending paediatrician in General Pediatric Clinic and the house officer on call in the Pediatric Emergency	Predictive value, Specificity and Sensitivity of Selected Overall Assessment Scores for	No serious limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
variables in assessing febrile children, Pediatrics, 65, 1090-1095, 1980 **Ref Id** 142067 **Country/ies where the study was carried out** USA **Study type** Diagnostic accuracy study **Aim of the study** - To identify the history and observation variables on which the 'instinctive' clinical judgment (made prior to performing a physical examination) of overall degree of illness of a febrile child is based - To study the relative importance of each of these variables in arriving at a judgment of overall degree of illness - To study interobserver agreement in scoring these variables and overall assessment and the influence of factors such as patient age, temperature, and level of physician training on observer	**Characteristics** Age: Children </=36 months (mean=13.4 months) Gender: Not reported Ethnicity: Not reported **Inclusion criteria** - Children </=36 months with a fever >/= 38.3C (101.0F) **Exclusion criteria** - Children who had been given antipyretics or tepid water sponges between observers	- Playfulness - Alertness - Consolability - Motor ability - Eating - Colour - Respirations - Hydration	Room were alerted when a child </=36 months with fever (>/=38.3C) entered - The initial observation could be made by either the attending paediatrician or the house officer. If the house officer made the initial observations, he or she would score the variables and overall impression and then perform a physical examination before the attending paediatrician observed the child. -The attending paediatrician scored the variables and overall impression without performing a physical examination. As two attending paediatricians made 90% of the observations, the technique of careful observation was regularly followed. This technique was also used by house officers. History variables were scored after each was discussed with the parents. - Children were followed as outpatients by telephone or a repeat clinic visit or as inpatients. Culture results and interpretations of chest roentgenograms were reviewed. After the follow-up observations were complete and all laboratory results were available, a final presumptive diagnosis was made. - In order to see which history and observation variables had the greatest impact on overall assessment, the scores of the house officers and attending paediatricians on each variable were correlated with that person's overall assessment of the same child using the Spearman rank correlation coefficient. - Interobserver agreement in scoring variables was examined by using weighted kappa. - Variables were evaluated for their specificity, sensitivity and predictive value for bacterial illnesses or pneumonia. A discriminate analysis using history and observation variables and overall assessment, with bacterial illness or pneumonia as outcome measures,	Bacterial Illnesses or Pneumonia Scores of 5,6 or 7 Attending paediatrician: PPV(%)=20 Specificity(%)=76 Sensitivity (%)=57 House officer: PPV(%)=14 Specificity(%)=74 Sensitivity (%)=38 Scores of 6 or 7 Attending paediatrician: PPV(%)=54 Specificity(%)=97 Sensitivity(%)=33 House officer: PPV(%)=31 Specificity(%)=94 Sensitivity(%)=24	**Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
agreement - To study the predictive power of judgment of overall degree of illness of more and less experienced observers in identifying children with more serious illnesses **Study dates** Not reported, however from August 1 1977 to February 1 1978, the faculty attending pediatrician in General Pediatric Clinic and the house officer on call in the Pediatric Emergency Room were alerted when a child </=36 months with fever (>/=38.3C) entered. **Source of funding** Not reported			was done using Datatext and SAS statistical programs.		
Full citation Young Infants Clinical Signs Study Group., Clinical signs that predict severe illness in children under age 2 months: a multicentre study, Lancet, 371, 135-142, 2008 **Ref Id** 151719	**Sample size** n=8889 **Characteristics** <u>Age:</u> <60 days <u>Gender:</u> Male (55%) Female (45%)	**Interventions** Temperature (<35.5C and >/= 37.5C)	**Details** - Infants under 60 days old who presented during study working hours were referred to the study triage person for screening. - An initial pilot test of 10-20 patients who were not included in data analysis was done at each site to confirm adequate training of study personnel and to test the study forms. Systematic sampling procedures were developed to ensure that an adequate number and balance of patients in each of the two age groups (0-6	**Results** <u>OR (95%CI) for association of temperature with severe illness requiring hospital admission (from an initial multiple regression model including 20 signs and symptoms)</u> <u>Temperature <35.5C</u> Age 0-6 days OR 16.6 (5.6-49.4) Age 7-59 days	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Bangladesh, Bolivia, Ghana, India, Pakistan and South Africa **Study type** Prospective observational cohort **Aim of the study** To provide evidence to support an Integrated Management of Childhood Illness (IMCI) referral checklist for sick neonates in the first week of life, and if possible, to improve the existing guidelines for infants aged 7-59 days. **Study dates** Not reported **Source of funding** This study was funded jointly by WHO, Boston University (through a Cooperative Agreement between Boston University and the Office of Health and Nutrition of the United States Agency for International Development), and Save the Children-US through a grant from the Bill	Ethnicity: Not reported **Inclusion criteria** Children under 60 days old brought to the hospital or outpatient clinic for an acute illness (not all had fever). **Exclusion criteria** Infants were excluded if they presented well for baby visits, did not reside in the defined study area (to ensure f/up), had been previously enrolled in this study, or were being seen for a repeat episode of the same illness. Additional exclusion criteria included the need for immediate cardiopulmonary resuscitation (an ethical imperative to ensure there was no delay in providing life-saving treatment), hospitalisation in the previous 2 weeks (except for delivery), referral from another health facility, an obvious lethal congenital malformation (e.g.: anencephaly) or if the caretaker was unwilling to provide written informed consent.		days and 7-59 days) would be enrolled at each site. - Eligible patients were referred to a trained primary health worker for initial assessment with a standardised proforma containing questions on maternal and birth history, history of the infant's present illness, weight and length, and documented physical signs as used in existing IMCI algorithms. - After this assessment, the patient was referred to a study paediatrician for evaluation and management. The paediatrician took a complete history and did a physical examination blinded to the primary health worker's findings. Procedures such as lumbar puncture, chest radiographs, were performed as required. - After reviewing the initial laboratory data and within 2 hours of initial assessment of the patient, the study paediatrician determined whether the infant had serious illness that required further hospital management or could be sent home with appropriate treatment. This assessment, i.e. whether the infant needed urgent, hospital-level care was the gold standard outcome for primary analysis. - The clinical course of hospitalised children was followed and the final outcome recorded. The caretakers of all patients who were sent home were advised to return for re-assessment in 48-72 hours. If they did not return for follow-up within 24 hours of the scheduled appointment, a nurse or paramedical worker attempted to contact the patient, and made a home follow-up visit on the next day, if necessary to determine the outcome. - The sensitivity, specificity and odds ratio for each sign and symptom individually and combined into algorithms to assess their value for predicting severe illness was calculated.	OR 7.2 (3.3-15.5) Temperature >/=37.5C Age 0-6 days 4.7 (2.8-8.0) Age 7-59 days 7.5 (5.0-11.4) OR (95%CI) for association of temperature with severe illness requiring hospital admission (independent clinical predictors) Temperature < 35.5C Age 0-6 days OR 9.2 (4.6 to 18.6) p < 0.0001 Age 7-59 days Not reported Temperature >/= 37.5C Age 0-6 days OR 3.4 (2.4 to 4.9) p < 0.0001 Age 7-59 days Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and Melinda Gates Foundation for the Saving Newborn Lives programme.					
Full citation Pantell,R.H., Newman,T.B., Bernzweig,J., Bergman,D.A., Takayama,J.I., Segal,M., Finch,S.A., Wasserman,R.C., Management and outcomes of care of fever in early infancy, JAMA, 291, 1203-1212, 2004 **Ref Id** 151967 **Country/ies where the study was carried out** United States **Study type** Prospective cohort study and diagnostic accuracy study **Aim of the study** To characterize the management and clinical outcomes of fever in infants, develop a clinical prediction model for the identification of bacteremia/bacterial meningitis, and compare the accuracy of various	**Sample size** n=3066 **Characteristics** Age: 3 months or younger Gender: Female (47%) Male (53%) Ethnicity: White, non-Hispanic (70%), Black (8%), Asian (2%), Hispanic (15%), Other/missing (5%) **Inclusion criteria** - Age 3 months or younger - Had been discharged from the hospital as a newborn - Had a temperature of 38C or greater either at home or in the clinician's office - No other major comorbidities (e.g.:	**Interventions** Appearance Ill family member Temperature Abnormal cry	**Details** - 573 members of the Pediatric Research in Office Settings (PROS) network from 219 practices submitted data on eligible infants - A prospective cohort study design was used to follow the episode of care for infants seen by PROS practitioners from February 28 1995, through April 25 1998 - Demographic and clinical data were recorded by office staff and clinicians on standard forms - Practitioners recorded clinical signs and symptoms and an overall assessment of clinical appearance before ordering laboratory tests and also answered questions about clinical appearance similar to those of the Yale Observation Scale with an addition of an item on respiratory distress - While other studies have addressed SBI as the main outcome variable, this paper focuses on occult infections that have generated the most uncertainty in developing clinical strategies; i.e., bacteremia with pathogenic organisms and bacterial meningitis - The accuracy of various clinical prediction models were compared by analysing several alternative scenarios.	**Results** Appearance moderately ill Raw data not reported Adjusted OR(95%CI): 1.79(0.95-3.38) p=0.07 Appearance very ill Raw data not reported Adjusted OR(95%CI): 8.90(3.34-23.69) p<0.001 Abnormal cry Raw data not reported Adjusted OR (95%CI): 2.23 (1.16 to 4.29) p<0.02 Temperature <38.0C Bacteremia or bacterial meningitis= 6/61 No bacteremia or bacterial meningitis= 829/2823 OR not reported p value not reported Temperature 38.0 to 38.4 Bacteremia or bacterial meningitis= 18/61 No bacteremia or bacterial meningitis= 1123/2823 OR not reported p value not reported Temperature 38.5 to 38.9C Bacteremia or bacterial meningitis= 27/61 No bacteremia or bacterial meningitis= 577/2823 Adjusted OR(95%CI): 2.37 (1.22 to 4.63)	**Limitations** Infants that were eligible but not enrolled were slightly older than enrolled infants, suggesting the true frequency of SBIs was less than reported **Other information** Multivariate predictors of bacteremia including laboratory data available in Table 9 of paper. Temperature data was missing from 182 patients, including 2 with bacteremia or bacterial meningitis

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strategies **Study dates** Not reported, however subjects included were infants seen by practitioners from February 28 1995 through to April 25 1998. **Source of funding** Supported by a grant from the Agency for Healthcare Research and Quality. Additional support from the Health Resources and Services Administration Maternal and Child Health Bureau.	congenital anomalies, extreme prematurity, conditions associated with organ system failure) **Exclusion criteria** Not reported			p=0.01 Temperature >/=39.0C Bacteremia or bacterial meningitis= 10/61 No bacteremia or bacterial meningitis= 294/2823 OR reported separately for 39.0 to 39.4C and 39.5 and higher (see below) p=0.12 Temperatures were not reported for 182 children (2 of which had bacteraemia/bacterial meningitis). The denominators used in the temperature data above reflect this Temperature 39.0 to 39.4C Raw data not reported Adjusted OR(95%CI): 1.84 (0.84 to 4.37) p value not reported Temperature >/=39.5C Raw data not reported Adjusted OR(95%CI): 3.61 (1.40 to 9.25) p=0.02	
Full citation Teach,S.J., Fleisher,G.R., Duration of fever and its relationship to bacteremia in febrile outpatients three to 36 months old. The Occult Bacteremia Study Group, Pediatric Emergency Care, 13, 317-319, 1997	**Sample size** n=6619 **Characteristics** <u>Age:</u> 3-36 months <u>Gender:</u> Not reported	**Interventions** -Mean temperature -Duration of fever	**Details** - The study population was drawn from 6680 patients previously enrolled in a prospective, multicentre, interventional trial conducted between November 1987 and May 1991 - During the enrolment process at each center, an attending paediatrician interviewed each patient's family prior to randomisation and noted both the date of enrolment and the date the current fever began	**Results** <u>Mean temperature</u> Occult bacteremia= 40C +/- 0.61C Without bacteremia= 39.8C +/- 0.55C p<0.001 <u>Duration of fever <1day</u> Bacteremia= 77/192 No bacteremia= 1941/6427 Sensitivity: 40.1% Specificity: 69.8%	**Limitations** It is possible that the recorded duration of fever lacks accuracy as the study authors were reliant on the caregivers' recall of the day on which fever

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Ref Id 151968 **Country/ies where the study was carried out** USA **Study type** Prospective observational cohort study **Aim of the study** To determine the relationship between the duration of fever as reported by caregivers and the likelihood of occult bacteremia in highly febrile young children **Study dates** Not reported however the study population was drawn from 6680 patients previously enrolled in an interventional trial conducted between November 1987 and May 1991. **Source of funding** Not reported	Ethnicity: Not reported **Inclusion criteria** - Age 90 days to 36 months - An initially recorded temperature of >/= 39.0C - A non-focal febrile illness as determined by a physical examination. A non-focal febrile illness was defined as excluding a focal, defined bacterial illness (pharyngitis, cellulitis, pneumonia) - A culture of blood drawn at the time of initial examination **Exclusion criteria** - A 'toxic' clinical appearance such that in the opinion of the attending paediatrician the child required admission to the hospital and intravenous antibiotics - A known or suspected allergy to amoxicillin or ceftriaxone - A focal bacterial infection other than otitis		- The duration of fever for each patient was grouped into the following categories: <1 day, 1-2 days, 2-3 days and so forth - Data were analysed using the Mann-Whitney U and the chi-squared tests for nonparametric data using the SPSS/PC statistical software package. Significance was defined as P<0.05	PPV: 3.8% NPV: 97.5% Duration of fever <2 days Bacteremia= 158/192 No bacteremia= 4735/6427 Sensitivity: 82.3% Specificity: 26.3% PPV: 3.2% NPV: 98.0% Duration of fever <3 days Sensitivity: 92.7% Specificity: 10.4% PPV: 3.0% NPV: 98.0% Duration of fever => 1 day Bacteremia= 115/192 No bacteremia= 4601/6427 Duration of fever => 2 days Bacteremia= 34/192 No bacteremia= 1692/6427	began. **Other information**

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	media - A specific viral infection (e.g.: varicella) - A known immunodeficiency or underlying chronic disease - Antibiotic therapy or immunization in the prior 48 hours - Lack of informed consent				
Full citation Stanley,R., Pagon,Z., Bachur,R., Hyperpyrexia among infants younger than 3 months, Pediatric Emergency Care, 21, 291-294, 2005 **Ref Id** 152048 **Country/ies where the study was carried out** USA **Study type** Retrospective case series **Aim of the study**	**Sample size** All febrile infants n=5279 Hyperpyrexic infants n=98 **Characteristics** Age: Median: 1.6 months (IQR:1.0-2.4 months) Gender: Not reported Ethnicity: Not reported **Inclusion criteria** Infants younger than 3 months with fever (temperature >/=38C) who presented to a large	**Interventions** -Temperature >40C -Temperature 38-39.9C	**Details** - All infants younger than 3 months with fever who presented to a paediatric emergency department were retrospectively identified - All infants were evaluated by a resident and an attending physician. Cases were identified from a computerized log that records triage temperatures. Laboratory data and emergency department discharge diagnoses were reviewed for all febrile infants. Hyperpyrexia was defined as temperature >/=40C. - Patients appearance was classified as 'well appearing' or 'ill appearing' based on the description in the medical record. - All febrile infants younger than 1 month are admitted for antibiotic therapy and febrile infants between 1 and 3 months who are well appearing and have no focus of infection, identified both by laboratory testing or physical examination, are discharged on antibiotic therapy pending culture results.	**Results** 2x2 table of temperature >40 or 38.8 to 39.9 for predicting presence of serious bacterial infection Temperature >40C Presence of SBI: 35/480 No SBI: 57/4799 Total: 92 Temperature 38-39.9C Presence of SBI: 445/480 No SBI: 4742/4799 Total: 5187	**Limitations** No serious limitations **Other information**

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To determine the prevalence of serious bacterial infection in infants younger than 3 months with fever >/=40C **Study dates** Not reported, however all infants were seen at the pediatric emergency department between January 1993-January 2000 **Source of funding** Not reported	urban paediatric emergency department over 84 consecutive months (January 1993-January 2000) **Exclusion criteria** Patients with underlying medical conditions, known immunodeficiency, or those who received antibiotics within 48 hours of emergency department presentation were excluded from the subgroup analysis of patients with hyperpyrexia.		- Serious bacterial infection (SBI) was defined as culture proven bacterial illness such as urinary tract infection (UTI), bacterial meningitis, bacteremia, bacterial enteritis. Focal pneumonia and cellulitis, although not culture proven bacterial infections, were also included as SBI. - UTI was defined as urine culture yielding >/=10 000 pure colony forming units/mL from a bladder catheterization or >/=1000 cfu/mL from a suprapubic aspiration. Otitis media was not considered an SBI. - Statistical analyses were conducted using SAS. Medians and interquartile ranges were provided for non-normal data. Mean values of interval data were compared between groups by using a 2-tailed student t test. X^2 and Fisher exact test were used to test nominal data. Confidence intervals for proportions were calculated.	Serious bacterial infections: UTI= 305 UTI with bacteraemia= 11 Meningitis= 10 Meningitis with bacteremia= 8 Bacteraemia without focal infection= 39 Pneumonia= 70 Cellulitis= 26 Bacterial enteritis= 11	
Full citation Alpert,G., Hibbert,E., Fleisher,G.R., Case-control study of hyperpyrexia in children, Pediatric Infectious Disease Journal, 9, 161-163, 1990 **Ref Id** 152049 **Country/ies where the study was carried out** USA **Study type** Retrospective case control	**Sample size** n=152 (76 cases, 76 controls) **Characteristics** <u>Age:</u> 3-36 months <u>Gender:</u> Males (51%) Females (49%) <u>Ethnicity:</u> Not reported **Inclusion criteria** Children aged 3-36 months with	**Interventions** Temperature (>/= 41.1C, 40.1C to 41.0C, 39.1C to 40C)	**Details** The study was performed in the emergency department of The Children's Hospital in Boston. Rectal temperatures were taken by the nursing staff with an electronic thermometer at time of triage for all children and documented in a log book. Patients aged 3-36months with temperatures>/=41.1C were identified from the log book. Controls were picked as the first patients in the appropriate age and temperature ranges appearing after the hyperpyrexic patients in the log book. Each child was routinely evaluated, laboratory tests and other procedures such as chest radiographs were determined by the treating physician. Long term follow-up was done by the authors through telephone contact with parents or the child's paediatrician and by review of the medical records.	**Results** 7 children had bacteremia 1 child had bacterial meningitis 7 children had UTI 16 children had pneumonia 197 had no SBI <u>Number of cases of bacteremia, bacterial meningitis, UTI, pneumonia in each temperature range</u> <u>Temperature >/=41.1C (n= 76)</u> Bacteremia: 1/7 (14%) Bacterial meningitis: 0/1 (0%) Urinary tract infection: 4/7 (57%) Pneumonia: 9/16 (56%) No serious bacterial infection: 62/197 (31%) <u>Temperature 40.1C-41.0C (n= 76)</u>	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study **Aim of the study** To test the association of hyperpyrexia with increased rates of bacteremia and serious bacterial illness in young children. **Study dates** April 1987 to December 1988 **Source of funding** Not reported	temperatures >/=41.1C. **Exclusion criteria** Not reported		Categorical variables were compared using chi-squared analysis with Yates continuity correction factor for any 2 group comparisons or by Fisher's exact test when the expected frequency in any cell was less than 5. Continuous variables were analysed with a one-way analysis of variance followed by the Scheffe test to determine significant differences between any pair of groups.	Bacteremia: 4/7 (57%) Bacterial meningitis:0/1 (0%) Urinary tract infection: 1/7 (14%) Pneumonia: 3/16 (14%) No serious bacterial infection: 68/197 (35%) <u>Temperature 39.1C-40.0C (n= 76)</u> Bacteremia: 2/7 (29%) Bacterial meningitis: 1/1 (100%) Urinary tract infection: 2/7 (29%) Pneumonia: 4/16 (25%) No serious bacterial infection= 67/197 (34%)	
Full citation Haddon,R.A., Barnett,P.L., Grimwood,K., Hogg,G.G., Bacteraemia in febrile children presenting to a paediatric emergency department., Medical Journal of Australia,Med.J.Aust., 170, 475-478, 1999 **Ref Id** 156120 **Country/ies where the study was carried out** Australia	**Sample size** n=534 **Characteristics** <u>Age:</u> 3-36 months <u>Gender:</u> Male (56%) Female (44%) <u>Ethnicity:</u> Not reported **Inclusion criteria** - Children aged 3-36	**Interventions** - Fever - McCarthy Score	**Details** - Subjects were drawn from children presenting at the Emergency Department of the Royal Children's Hospital, Melbourne. - Demographic and clinical details including provisional diagnosis, investigations, treatment and follow-up arrangements were recorded by Emergency Department staff. The child's general condition was assessed on the McCarthy Observation Scale where a score </=10 is associated with a low risk of serious illness. Medical staff was asked to predict the likelihood of bacteremia on a scale of 1-5. - Each subject had blood taken during the presentation for a full blood count and culture. Blood culture specimens were inoculated into liquid culture medium and incubated for 5 days. Bacteremia was diagnosed if	**Results** <u>Comparison of children with and without bacteremia (mean and standard deviation)</u> <u>Fever</u> Bacteremia: 39.7 (0.39) No bacteremia: 39.7 (0.55) P value: 0.91 <u>McCarthy Score</u> Bacteremia: 7.0 (1.5)	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Prospective observational case study **Aim of the study** To determine the prevalence of bacteremia in young febrile children presenting to a pediatric emergency department. **Study dates** May 1996-May 1997 **Source of funding** Not reported	months - Temperature >/=39C recorded by tympanic thermometry in the Emergency Department, regardless of presumed clinical source of the fever **Exclusion criteria** - Children with varicella, croup or herpes gingivostomatitis		blood culture showed growth of a pathogenic organism. - Families of children who were discharged but had positive blood cultures were telephoned the next day. - Other investigations and management decisions were at the discretion of the treating doctors. - Final diagnoses for each illness episode were determined by one of the investigators from a combination of presenting symptoms and signs, the treating doctor's presumptive diagnosis, results of investigations and chart review. - In weeks 5 and 6 of the study, chart and computer records of all eligible patients were reviewed to assess the enrolment rate. - Statistical analyses were performed using SPSS. Means and proportions were compared by standard tests (x^2 and t-tests) and 95%CIs for proportions by the exact binomial method.	No bacteremia: 7.4 (1.9) P value: 0.45 Score of 4-5 on likelihood of bacteraemia With bacteraemia= 1/18 Without bacteraemia= 19/358 Duration of fever =< 12 hours Bacteraemia= 10/18 No bacteraemia= 93/496 > 12 hours Bacteraemia= 8/18 No bacteraemia= 403/496	
Full citation Singhi,S., Kohli,V., Ayyagiri,A., Bacteremia and bacterial infections in highly febrile children without apparent focus, Indian Pediatrics,Indian Pediatr., 29, 1285-1289, 1992 **Ref Id** 156122 **Country/ies where the study was carried out**	**Sample size** n=100 **Characteristics** Age: 1 month-3 years (mean age= 11.7 months +/- 8.5 months) Gender: Male (55%) Female (45%) Ethnicity: Not reported	**Interventions** Temperature (C)	**Details** - A detailed history and physical examination were done at admission. Venous blood was obtained by standard methods. - Urine culture, and CSF analysis and culture were done in all the infants below one year and in older children wherever indicated. - In the hospital, daily physical examination was done and progress noted. All the management decisions were made by the treating physicians and were independent of the study. - On the basis of the final diagnosis, the data was	**Results** Culture +ve bacteremia Temperature in degrees (mean+/-SD): 38.8+/-0.3 Serology +ve bacteremia Temperature in degrees (mean+/-SD): 38.7+/-0.2 UTI Temperature in degrees (mean+/-SD):	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
India **Study type** Prospective study **Aim of the study** To find: i) the prevalence and causative organisms of bacteremia and bacterial infections in febrile children without an identifiable focus of infection attending the Pediatric Emergency Service ii) the usefulness of total leucocyte count, absolute neutrophil count and micro-ESR in early diagnosis of bacterial infection **Study dates** January 1989-July 1990 **Source of funding** Not reported	**Inclusion criteria** - Axillary temperature of more than 38.5C (or rectal >/=39C) without any apparent focus of infection on history and physical examination - A normal chest X-ray and a peripheral blood film negative for malaria parasite - Fever </=3 days duration **Exclusion criteria** - Patients with a neoplastic and immunosuppressive disease - Chronic diseases such as nephrotic syndrome, liver disease or heart disease - Those who had received prior antibiotic therapy		divided into 3 groups; Group one-bacterial infection, Group two-presumed bacterial infection and Group 3 non-bacterial febrile illness. The group with bacterial infections was further subdivided into bacteremia (blood culture +ve or serology +ve) and UTI (urine culture +ve). Presumed bacterial infection included otitis media and pyomeningitis. -The diagnosis of pyomeningitis and otitis media was not apparent at the time of admission but was arrived at, respectively after CSF analysis and clinical examination on follow up. - Children with non-bacterial illness were those whose blood, urine and CSF cultures were sterile and the seriological tests were negative. - The means and standard deviations were calculated for total leucocyte count (TLC), absolute neutrophil count (ANC) and micro-ESR (m-ESR) and temperature within various groups, and compared by t test. - Specificity, sensitivity and predictive values of the above tests were computed for their ability to discriminate children with bacteremia.	38.8 +/-0.1 <u>Otitis media</u> Temperature in degrees (mean+/-SD): 38.8+/-0.1 <u>Pyomeningitis</u> Temperature in degrees (mean+/-SD): 38.7+/-0.2 <u>Non-bacterial illnesses</u> Temperature in degrees (mean+/-SD): 38.8+/- 0.15	
Full citation Teach,S.J., Fleisher,G.R., Efficacy of an observation scale in detecting bacteremia in febrile children three to thirty-six months of age, treated as	**Sample size** n=6680 **Characteristics**	**Interventions** <u>Yale Observation Scale</u> - Quality of cry	**Details** - The study population was drawn from 6680 patients prospectively enrolled in a prior multicentre trial of the use of parenteral versus oral antibiotics for the prevention of bacterial complications in children with	**Results** 192 had bacteremia 6419 children did not have bacteremia <u>YOS score > 6</u>	**Limitations** This study applied the YOS to a population it was not originally

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outpatients. Occult Bacteremia Study Group, Journal of Pediatrics,J.Pediatr., 126, 877-881, 1995 **Ref Id** 156123 **Country/ies where the study was carried out** USA **Study type** Retrospective analysis of data from a prospective intervention study **Aim of the study** To assess the efficacy of the Yale Observation Scale in detecting occult bacteremia in febrile, ambulatory pediatric patients with no apparent signs or symptoms of severe infection and with no focal infection. **Study dates** November 1987-May 1991 **Source of funding** Not reported	Age: 3-36 months Gender: Not reported Ethnicity: Not reported **Inclusion criteria** - Age from 90 days to 36 months - Temperature of at least 39C - A non-focal febrile illness as determined by a physical examination and a blood sample taken for culture at the time of initial examination (a non-focal febrile illness was defined as excluding a focal, defined bacterial illness (E.g.: pharyngitis, cellulitis, pneumonia) **Exclusion criteria** - A toxic clinical appearance such that in the opinion of the attending paediatrician the child required admission to the hospital and intravenous	- Reaction to parent stimulation - State variation - Colour - Hydration - Response (talk, smile) to social overtures	occult bacteremia. - As part of the initial multicentre study design, an attending paediatrician enrolled and examined each patient in standard fashion with the YOS before patients were randomly assigned to receive an antibiotic regimen. - Data were analysed with the Mann-Whitney U test for unpaired nonparametric data. Aggregate mean ranks were compared using SPSS. - Significance was defined at a p value <0.05.	Patients with bacteremia: n=55/192 (28.6%) Patients without bacteremia: n=1122/6419 (17.5%) Sensitivity (%): 28.6 Specificity (%): 82.5 PPV (%): 4.7 NPV (%): 97.4 YOS score > 8 Patients with bacteremia: n=32/192 (16.7%) Patients without bacteremia: n=522/6419 (8.1%) Sensitivity (%): 16.7 Specificity (%): 91.9 PPV (%): 5.8 NPV (%): 97.3 YOS score > 10 Patients with bacteremia: n=10/192 (5.2%) Patients without bacteremia: n=210/6419 (3.3%) Sensitivity (%): 5.2 Specificity (%): 96.7 PPV (%): 4.5 NPV (%): 97.1 YOS score > 12 Patients with bacteremia: n=1/192 (0.5%) Patients without bacteremia: n=75/6419 (1.2%) Sensitivity (%): 0.5 Specificity (%): 98.8 PPV (%): 1.3 NPV (%): 97.1	designed for - detection of occult bacteremia in ambulatory, febrile patients who are considered to have neither a toxic nor a serious focal illness. This is a specific, selected population. **Other information** Excluded from analysis Lost blood cultures= 43 children Incomplete YOS score= 23 children Insufficient follow-up= 1 child

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	antibiotic therapy - A known or suspected allergy to amoxicillin or ceftriaxone - A focal bacterial infection other than otitis media - A specific viral infection (e.g.: varicella) - A known immunodeficiency or underlying chronic disease that would affect the approach to an uncomplicated febrile illness - Antibiotic therapy or immunization during the prior 48 hours - Lack of informed consent				
Full citation Teele,D.W., Pelton,S.I., Grant,M.J., Herskowitz,J., Rosen,D.J., Allen,C.E., Wimmer,R.S., Klein,J.O., Bacteremia in febrile children under 2 years of age: results of cultures of blood of 600 consecutive febrile children seen in a "walk-in" clinic, Journal of Pediatrics, 87, 227-230,	**Sample size** n=600 **Characteristics** Age: <2 years Gender: Not reported	**Interventions** Temperature <38.9C (rectal) Temperature >/=38.9C (rectal)	**Details** - Seven participating physicians obtained pre-treatment cultures of blood from children seen by them at the Pediatric 'Walk-In' clinic of the Boston City Hospital. - All children without prior medical evaluation or referral from other physicians or from other clinics were seen by the primary physician. - The age, date of visit, rectal temperature, peripheral white blood cell count, interpretation of chest roentgenofram, clinical diagnosis, results of all	**Results** When more than one focus of infection was present, the child was placed in the most severe category Analysis of features associated with bacteraemia: TEMPERATURE <38.9C (RECTAL) Upper respiratory infection/fever of	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
1975 **Ref Id** 156145 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** To identify clinical and laboratory features associated with bacteremia in febrile children. **Study dates** January 1973-June 1974 **Source of funding** Supported, in part, by Research Grant RO1-A1-0023 from the National Institute of Allergy and Infectious Diseases.	Ethnicity: Not reported **Inclusion criteria** - Children under 2 years of age - Rectal temperature of 38.3C (101F) or higher **Exclusion criteria** Not reported		bacteriologic cultures, and the clinical course were all recorded. - Venous blood was obtained in the routine manner after skin preparation. - The clinical diagnoses were made by the primary physician and included the following: 1) Upper respiratory infection/fever of unknown origin- the category of upper respiratory infections included some patients with minimal signs and no other apparent explanation for fever. 2) otitis media-diagnosed on the basis of the appearance and mobility of the tympanic membrane 3) pharyngitis- when considered the source of fever 4) pneumonia-diagnosed on the basis of the clinical examination and chest roentgenogram 5) Miscellaneous-other infections including gastroenteritis, soft tissue infection and childhood exanthems. - When more than one focus of infection was present, the child was placed in the most severe category. - Patients from whom any bacterial species was isolated from the blood were recalled, re-examined, and re-evaluated by the primary physician as soon as possible.	unknown origin Positive culture of the blood at initial visit: 0 Total number of children cultured: 44 Pneumonia Positive culture of the blood at initial visit: 0 Total number of children cultured: 20 Pharyngitis Positive culture of the blood at initial visit: 0 Total number of children cultured: 19 Otitis media Positive culture of the blood at initial visit: 0 Total number of children cultured: 35 Other Positive culture of the blood at initial visit: 0 Total number of children cultured: 23 All Positive culture of the blood at initial visit: 0 Total number of children cultured: 141	

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				TEMPERATURE >/=38.9C (RECTAL) Upper respiratory infection/fever of unknown origin Positive culture of the blood at initial visit: 5 Total number of children cultured: 129 Pneumonia Positive culture of the blood at initial visit: 9 Total number of children cultured: 80 Pharyngitis Positive culture of the blood at initial visit: 1 Total number of children cultured: 64 Otitis media Positive culture of the blood at initial visit: 2 Total number of children cultured: 131 Other Positive culture of the blood at initial visit: 2 Total number of children cultured: 55 All Positive culture of the blood at initial visit:	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				19 Total number of children cultured: 459	
Full citation Tal,Y., Even,L., Kugelman,A., Hardoff,D., Srugo,I., Jaffe,M., The clinical significance of rigors in febrile children, European Journal of Pediatrics, 156, 457-459, 1997 **Ref Id** 172232 **Country/ies where the study was carried out** Israel **Study type** Prospective cohort study **Aim of the study** To evaluate the significance of rigor as a predictor of bacterial infection in hospitalised febrile infants and children. **Study dates** January to October 1993	**Sample size** 434 children - 100 with rigors and 334 matched controls **Characteristics** 6 months to 16 years (average 6.4 years) 52 males (52%) in study group **Inclusion criteria** Febrile illness Temperature of 38.5 or higher Rigor **Exclusion criteria** Febrile seizures	**Interventions** Compares the incidence of bacterial illness in febrile children with and without rigors	**Details** 60% of cases of rigor were parent/caretaker reported, 40% were witnessed by medical personnel. When in doubt, cases were not included All patients were admitted for hospitalisation to the paediatric department, none were discharged from the emergency room All children underwent routine clinical evaluation by four paediatricians: complete blood count, ESR, urinalysis, blood and urinary cultures, and chest roentgenograms. Lumbar punctures were done when clinically indicated. Clinical state of the patients was determined using the Yale Toxicity Score by the same four paediatricians After recruiting a child with rigors, the subsequent 3 or 4 febrile children without chills and with a reason to be admitted, matched for age, sex, degree of fever and clinical state (Yale toxicity score), were included The bacterial infection group consisted of children with proven bacteriological infection, and presumed bacterial infection - proven bacterial infection was defined by one or more positive bacterial cultures (blood, urine, and/or stools). Urinary tract infection was diagnosed under 4 years of age by a colony count of $>10^3$/ml in a urinary sample obtained by either catheter or suprapubic aspiration, and in children over 4 years by a colony count of $>10^5$/ml in a midstream specimen. Presumed bacterial infections were those clinical diagnosis which are often associated with a bacterial aetiology, although a viral cause cannot be definitely excluded.	**Results** Rigor (n= 100): Pneumonia= 25 (25%) AOM= 26 (26%) UTI= 9 (9%) Ge Shiqella= 1 (1%) Abscess= 3 (3%) Occult bacteraemia= 2 (2%) Typhoid fever= 1 (1%) Total presumed bacterial= 67 (67%) No rigor (n= 334): Pneumonia=60 (18%) AOM= 77 (23%) UTI= 13 (4%) Ge Shiqella= 2 (0.5%)	**Limitations** Restricted to children referred for hospitalisation **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding None reported			Presumed non bacterial infection - acute febrile illness where neither the clinical examination nor bacterial cultures indicated a probable bacterial aetiology Statistical analysis was done using the chi square test and the Fisher exact test when the expected values were less than 5	Abscess= 17 (5%) Occult bacteraemia= 0 (0%) Typhoid fever= 0 (0%) Total presumed bacterial= 169 (51%)	
Full citation Gomez,B., Mintegi,S., Rubio,M.C., Garcia,D., Garcia,S., Benito,J., Clinical and analytical characteristics and short-term evolution of enteroviral meningitis in young infants presenting with fever without source, Pediatric Emergency Care, 28, 518-523, 2012 **Ref Id** 191027 **Country/ies where the study was carried out** Spain **Study type** Retrospective cross-sectional study **Aim of the study** To describe characteristics of enteroviral meningitis diagnosed in a paediatric emergency department	**Sample size** n= 1348 **Characteristics** Not specified **Inclusion criteria** Younger than 90 days Fever without source Measured temperature of 38.0C or greater at home or upon arrival at the paediatric emergency department **Exclusion criteria** Not specified	**Interventions** Irritable	**Details** Retrospective study. All children received clinical care as determined by the emergency physician. The hospital algorithm for management of these children recommends urine dipstick testing, complete blood count, C-reactive protein, pro-calcitonin, blood culture, and urine culture for all children. The practice of lumbar puncture, together with Gram stain, bacterial and viral cultures, and enteroviral polymerase chain reaction (PCR) is recommended in infants younger than 15 days, in those not well-appearing, and in those with abnormal laboratory tests. If an infant older than 15 days is well-appearing, and all ancillary tests are normal, it is recommended that the patient is discharged without antibiotic treatment after several hours of observation in the PED (generally up to 24 hours). For infants younger than 15 days, for those with abnormal laboratory tests, and when the clinical situation worsens during the patient's stay in the observation unit, hospital admission is recommended. Well appearing infants who are 16 to 30 days old are monitored in the observation unit and they are either hospitalised or discharged depending on their clinical evolution. The electronic log of visits to the PED was reviewed monthly by a paediatric emergency physician to ensure proper identification of all potentially eligible febrile	**Results** Final diagnoses for the 1348 children: No SBI= 1100 (82%) (fever without source= 862, flu= 89, enteroviral meningitis= 65, nonspecific meningitis= 42, other= 42) SBI= 248 (18%) (UTI= 218, occult bacteraemia= 10, UTI and bacteraemia= 9, sepsis= 4, bacterial meningitis= 4, cellulitis= 2, acute otitis media= 1) Irritability: Viral meningitis= 16/63 Nonspecific meningitis= 8/38 Fever without source= 46/208	**Limitations** No serious limitations **Other information** Most of these children were included in Gomez (2010), which reports different symptoms and signs. Data for 'well-appearing' was also reported in this study. However, as it was reported in Gomez (2010) in a way that is more applicable to the current review, the data on 'well-appearing' from the 2012 study was not included in the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
among infants younger than 3 months with fever without source and its short-term evolution **Study dates** September 2003 to August 2009 **Source of funding** None reported			infants and to assess the capture rate for the study. Electronic PED medical records were reviewed. Final patient discharge charts were reviewed when infants were admitted to the hospital. If they were not, a follow-up phone call was done during the month following the visit to the PED to monitor their evolution. Both charts revision and phone calls were made by resident doctors, after training. A standardised form to abstract the data was used. Doctors were blinded to study objectives during the chart revision. The hospital database was checked to review any new, unscheduled emergency visits after the initial discharge.		current review. Fever without source defined as axillary or rectal temperature at home or rectal temperature at the PED 38C or greater, without catarrhal or respiratory symptoms/signs, or a diarrheal process, in patients with normal physical examination, according to the diagnostic codes issued by the Spanish Society of Paediatric Emergencies. Well-appearing defined by a paediatric emergency physician with a normal paediatric assessment triangle within the first hour after attending the PED. Appearance, respiratory and circulatory items had to be

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					assessed to be normal, and data had to be reflected on the patient's charts. Enteroviral meningitis: positive enteroviral culture of positive enteroviral PCR in CSF Nonspecific meningitis: pleocytosis with negative CSF bacterial and viral cultures and negative enteroviral PCR in CSF
Full citation Zarkesh,M., Hashemian,H., Momtazbakhsh,M., Rostami,T., Assessment of febrile neonates according to low risk criteria for serious bacterial infection, Iranian Journal of Pediatrics, 21, 436-440, 2011 **Ref Id** 191096 **Country/ies where the**	**Sample size** 202 children **Characteristics** 107 males, 95 females 83 infants were 7 days old or younger, 119 infants were older than 7 days old **Inclusion criteria** Rectal temperature of	**Interventions** Temperature	**Details** Approved by School of Medicine Ethics Committee, Guilan University of Medical Sciences Reviewed the records of all febrile neonates (28 days old or younger) seen in the emergency room and admitted at 17 Shahrivar Children's Hospital in Rasht, Iran. All febrile neonates underwent the same sepsis workup, including blood, urine and cerebro-spinal fluid cultures, complete blood cell count with differential evaluation, c-reactive protein, urine analysis with microscopic examination of urinary sediment, chest x-ray (when respiratory signs or symptoms were present), and stool examination and culture (only for infants with	**Results** 38 (19%) neonates had SBI Temperature (rectal): 38.5 to 39.4C With SBI= 29/38 Without SBI= 125/164 ≥39.5C With SBI= 9/38 Without SBI= 39/164	**Limitations** No serious limitations **Other information** 51 records were excluded for incomplete data

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out Iran **Study type** Retrospective review **Aim of the study** To assess the reliability of low risk criteria to exclude serious bacterial infection in febrile neonates. **Study dates** January 2004 to January 2009 **Source of funding** None reported	38.5C or higher measured in the emergency room **Exclusion criteria** Prematurity Positive history of admission Receipt of antibiotics Chronic disease		diarrhoea). Urine culture was obtained by suprapubic bladder aspiration or by transient bladder catheterisation. All neonates were treated with systemic antibiotics after obtaining cultures. A questionnaire was designed for each neonate. SBI was defined as: 1) growth of any bacterial pathogen in one or more of CSF, blood, urine, stool cultures 2) Any disease commonly associated with bacterial pathogens including pneumonia or soft tissue infections (mastitis, cellulitis, omphalitis). Pneumonia was diagnosed according to clinical and radiological findings in chest x-ray. Otitis media was not considered as an SBI. Isolation of any bacteria from a bladder aspirate or counts of 10^3 or higher colony-forming units per millilitre of catheterised urine was considered as UTI.		
Full citation Nijman,R.G., Zwinkels,R.L., van,Veen M., Steyerberg,E.W., van der,Lei J., Moll,H.A., Oostenbrink,R., Can urgency classification of the Manchester triage system predict serious bacterial infections in febrile children?, Archives of Disease in Childhood, 96, 715-722, 2011 **Ref Id**	**Sample size** 1255 children **Characteristics** Median age 1.8 years (IQR 0.9 to 3.9) Boys= 743 (59%) Age: 1 month to 1 year= 361 (29%) 1 year to 2 years= 306 (24%)	**Interventions** Shortness of breath Diarrhoea and vomiting Abdominal pain Rashes Unwell Ear problems Urinary problems Temperature in the ED	**Details** This study was conducted with the approval of the Ethics Committee, Erasmus MC, Rotterdam, and The Netherlands. The requirement for informed consent was waived. Patient characteristics, presenting symptoms and signs and the triage data of all patients visiting the ED is registered routinely in an electronic patient record. Final diagnoses were classed as either SBI or non-SBI. SBI= pneumonia, meningitis, septicaemia, urinary tract infection, and other less frequent diagnoses such as erysipelas, cellulitis, bacterial gastroenteritis, cellulitis orbitae, bacterial upper airway infection, ethmoiditis, arthritis and osteomyelitis. Final diagnoses were determined by positive bacteriological cultures of blood,	**Results** 131 children had SBI 1124 children did not have SBI Shortness of breath SBI= 36/131 (28%) No SBI= 138/1124 (13%) Diarrhoea and vomiting SBI= 8/131 (6%) No SBI= 106/1124 (10%) Abdominal pain SBI= 6/131 (5%)	**Limitations** No serious limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
191687 **Country/ies where the study was carried out** The Netherlands **Study type** Prospective observational study **Aim of the study** To evaluate the discriminative ability of the Manchester Triage System to identify serious bacterial infections in children with fever in the emergency department and to study the association between predictors of SBI and discriminators of MTS urgency of care. **Study dates** January 2008 to July 2009 **Source of funding** One author is supported by a grant from ZonMW, the Dutch Organisation for Health Research and Development, and Erasmus MC Doelmatigheir. Another author is supported by an unrestricted grant from Europe Container	2 to 5 years= 373 (30%) 5 to 16 years= 215 (17%) **Inclusion criteria** A temperature of $\geq$ 38.5C, a recent high fever or fever as a reason for referral 1 month to 16 years old **Exclusion criteria** Consecutive visits of children within 5 days of the first presentation with the same reason for consultation (n= 121) (these children were only considered once in the analysis - final diagnoses were based on available data from all consecutive visits) Children with missing data (n= 1) Children with chronic comorbidity who have an increased risk of acquiring SBIs or developing severe complications and who visited a (subspecialist) paediatrician at least twice in the preceding year (n= 534)		urine, stool and ear, nose or throat, or radiological findings according to a reference standard. The reference standard included a follow-up period for all discharged patients to rule out the possibility of missed SBI and to avoid verification bias. Follow-up consisted of checking for consecutive ED visits and hospital admission in a 1-week period after the first visit. If the final diagnosis was inconclusive, a consensus diagnosis was reached by the investigators.	No SBI= 39/1124 (4%) Rashes SBI= 4/131 (3%) No SBI= 30/1124 (3%) Unwell SBI= 2/131 (2%) No SBI= 29/1124 (3%) Ear problems SBI= 5/131 (4%) No SBI= 24/1124 (2%) Urinary problems SBI= 11/131 (9%) No SBI= 16/1124 (1%) Temperature in the ED SBI= 39.3 (38.6 to 39.8) No SBI= 38.9 (38.1 to 39.6) p= 0.000	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Terminals B.V.					

Chapter 5

Heart rate

Review question

The predictive value of heart rate, including:

- how heart rate changes with temperature?
- whether heart rate outside the normal range detects serious illness?
- whether heart rate and temperature outside normal range detects serious illness?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Davies,P., Maconochie,I., The relationship between body temperature, heart rate and respiratory rate in children, Emergency Medicine Journal, 26, 641-643, 2009 **Ref Id** 118906 **Country/ies where the study was carried out** UK **Study type** Retrospective observational study. **Aim of the study** The aim of this study was to describe and quantify the effect that increasing body	**Sample size** 21,033 children **Characteristics** Age: median, range 36 (0–198) months. Gender: Not reported. Diagnosis: Not reported **Inclusion criteria** Children attending a paediatric emergency department but that were not admitted to hospital. **Exclusion criteria** All children admitted to hospital were excluded from the study.	**Interventions** **Diagnostic evaluation** Measuring heart rate in conjunction with temperature to detect serious illness.	**Details** Recruitment: 63,857 children attending a paediatric emergency department were examined. 31,851 had a complete set of data on pulse, temperature and age. 21,033 of these children were not admitted (and therefore analysed). 14,487 of the non-admitted children had a complete data on respiratory rates. Methods: Age, heart rate and temperature data were collected. These were measured in the standard way by the healthcare professionals. Temperature was taken tympanically, heart rate usually by pulse oximeter and manually. The time periods used in the study was selected by the availability of the relevant databases. Statistical analysis: The data were analysed using quantile regression. Statistical modelling developed a	Results **Expected parameter value = Body temperature x a + Age x b + Age2 x c + constant** The individual pulse data were adjusted to the median age of 36 months and plotted against temperature. The value of the constant a, b and c for the 5th, 25th, 50th, 75thand 95th centiles are reported below: 5th centile: a = 9.468 b = -0.6543 c = 0.001998 constant = 230.2. 25th centile: a = 10.99; b = -0.7040 c = 0.002198 constant = 270.1. 50th centile: a = 11.44 b = -0.7393 c = 0.002374 constant = 274.9. 75th centile:	**Limitations** Retrospective study type. There may have been variation in how the measurements of pulse and temperature have been taken. Large spread in the normal ranges of heart rate. Indirectness: The study includes children older than 5 years of age. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
temperature has on heart rate and respiratory rate in children attending a paediatric emergency department. **Study dates** In UK between 2003 and 2006. **Source of funding** Not reported.			best fit equation in four parts: body temperature in ^{o}C, age in months and age^{2} in months^{2}.	a = 11.35 b = -0.7615 c = 0.002474 constant = 258.8. 95th centile: a = 9.397 b = -0.8494 c = 0.002848 constant = 163.3. The temperature multiplier a, has a mean increase of 10.52 beat per minute (bpm) through the centile.	
Full citation Thompson,M., Harnden,A., Perera,R., Mayon-White,R., Smith,L., McLeod,D., Mant,D., Deriving temperature and age appropriate heart rate centiles for children with acute infections, Archives of Disease in Childhood, 94, 361-365, 2008 **Ref Id** 119152 **Country/ies where the study was carried out** 10 surgeries in Oxfordshire, Buckinghamshire and Somerset, and two out-ofhours centres in Oxfordshire. **Study type**	**Sample size** 1589 children. **Characteristics** Age: 3 months–10 years. Gender: Male 1027 (53.1%); Female 906 (46.9%). Diagnosis: 859 children (54.1%) had upper respiratory tract infections. 215 children (13.5%) had a nonspecific viral illness. 125, 7.9% had respiratory tract infections. 82, 5.2% had or diarrhoea and/or vomiting. Setting: Presenting to primary care with self-limiting infections.	**Interventions** **Diagnostic evaluation** Measuring heart rate in conjunction with temperature to detect serious illness.	**Details** Recruitment: 1933 children presenting with suspected acute infections were recruited from in-hours general practice surgeries (1050 or 54.3%) or out-of-hours centres (883 or 45.7%). Three groups of children were excluded before creating the centile charts. 1589 children were used to create the centile charts. The final sample used to create the centile charts (n=1589) had the following age distribution: 254, 3–12 months; 254, 1–2 years; 538, 2–5 years; and 543, 5–10 years. A total of 622 children had a temperatures under 37.0^{o}C, 609 had temperatures between 37.0^{o}C and 37.9^{o}C, 221 had temperatures between 38.0^{o}C and 38.9^{o}C, and 137 had temperatures of 39.0^{o}C or	**Results** Heart rate was negatively correlated with age (r = -0.62) and positively correlated with temperature (r = 0.49). The correlation between heart rate and temperature was significant for all four age groups but was smaller in children aged ,1 year (r = 0.41) and 1–2 years (r = 0.42) than in those in the 2–5-year (r = 0.65) or 5–10-year (r = 0.59) age group. The incremental increases of heart rate for each increment in 1 C^{o} of temperature: Combined group of 1589 children: 13.7 bpm (95% CI 12.5 to 14.9); Age 3–12 months:	**Limitations** Recruitment was not systematic, the proportion of children consulting out-of-hours care was high, and the researcher set the minimum recruitment targets for each age–temperature combination. Large spread of the heart rate values expected at different temperatures Indirectness: The study includes children older than 5 years of age. **Other information** 1) In the first year all children were recruited. In the final 18 months children younger than 2 years of age and/or with temperatures over 38.0^{o}C were prioritised to try to achieve a recruitment target of 30–60 children in each age–temperature category.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Prospective cross–sectional primary care study. **Aim of the study** The aim of the study to describe the reference range for heart rate in children aged 3 months–10 years presenting to primary care with self-limiting infections. **Study dates** December 2003 to March 2006. **Source of funding** This study was funded by the Medical Research Council and by the Thames Valley Research and Development Consortium support for science funding.	**Inclusion criteria** Children presenting to primary care with suspected acute infection. **Exclusion criteria** Children who subsequently attended hospital. Children without a final diagnosis of acute infection.		higher. Methods: The clinical diagnosis made at presentation was recorded and temperature was taken (see other information). The medical records were subsequently reviewed for each child to identify any hospital attendances and those children were excluded from the study. Statistical analysis: The correlation coefficient was calculated using Spearman's r (rank correlation) for nonparametric variables and linear regression to estimate regression coefficients for the relationship between heart rate and temperature in each age group. The median and upper centiles (75th, 90th and 97th) of heart rate at a given temperature for children were calculated in each of the four age groups, based on the method of Cole and Green.	12.1 bpm (95% CI 9.2 to 15.0); Age 1–2 years: 9.9 bpm (95% CI 7.3 to 12.5); Age 2–5 years: 14.1 bpm (95% CI 12.7 to 15.5); Age 5–10 years: 14.1 bpm (95% CI 12.6 to 15.6). The heart rate values expected at different temperatures in children 3 months–10 years of age with acute self-limiting infections in primary care are presented below: **Age 3–12 months** Temperature 36.0 – 36.9^{o}C*;* Heart rate (bpm): 50th centiles; 75th centiles; 90th centiles; 95th centiles = 138; 151; 164; 178. Temperature 37.0 – 37.9^{o}C*;* Heart rate (bpm): 50th centiles; 75th centiles; 90th centiles; 95th centiles = 154; 166; 179; 192. Temperature 38.0 – 38.9^{o}C*;* Heart rate (bpm): 50th centiles; 75th centiles; 90th centiles; 95th centiles = 169; 182; 194; 206. Temperature 9.0 – 39.9^{o}C*;* Heart rate (bpm): 50th centiles; 75th centiles; 90th centiles; 95th centiles = 174; 192; 204; 215. **Age 1–2 years**	2) The thermometer was place high in the axilla, adduct and hold the arm close to the chest wall for the 10 s reading time. The heart rate was measured using Nonin 8500 pulse oximeters.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Temperature 36.0 – 36.9°C; Heart rate (bpm): 50th centiles; 75th centiles; 90th centiles; 95th centiles = 133; 146; 160; 175. Temperature 37.0 – 37.9°C; Heart rate (bpm): 50th centiles; 75th centiles; 90th centiles; 95th centiles = 147; 160; 173; 186. Temperature 38.0 – 38.9°C; Heart rate (bpm): 50th centiles; 75th centiles; 90th centiles; 95th centiles = 156; 170; 183; 195. Temperature 39.0 – 39.9°C; Heart rate (bpm): 50th centiles; 75th centiles; 90th centiles; 95th centiles = 164; 178; 191; 202. **Age 2–5 years** Temperature 36.0 – 36.9°C; Heart rate (bpm): 50th centiles; 75th centiles; 90th centiles; 95th centiles = 116; 126; 137; 148. Temperature 37.0 – 37.9°C; Heart rate (bpm): 50th centiles; 75th centiles; 90th centiles; 95th centiles = 132; 142; 153; 164. Temperature 38.0 – 38.9°C; Heart rate (bpm): 50th centiles; 75th centile; 90th centiles; 95th centiles = 144; 154; 164; 175. Temperature 39.0 – 39.9°C; Heart rate (bpm): 50th centiles; 75th centiles; 90th centiles; 95th centiles = 155; 164; 174; 184.	
Full citation Brent,A.J., Lakhanpaul,M., Ninis,N., Levin,M., MacFaul,R., Thompson,M., Evaluation of temperature-pulse centile charts in identifying serious bacterial	**Sample size** **First study**: 1360 children. **Second study:** 325 children.	**Interventions** **Diagnostic evaluation** Measuring heart rate in conjunction with temperature to	**Details** **First study:** Recruitment: Data were collected of children presenting with clinical symptoms and signs, laboratory indices, treatment and final diagnosis were	**Results** **Fist Study:** Scatter graphs of temperature and pulse for children presenting to the emergency department with and without	**Limitations** **First study:** Imprecision: The lack of a clear, gold-standard definition of severe bacterial illness.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
illness: observational cohort study, Archives of Disease in Childhood, 96, 368-373, 2011 **Ref Id** 138355 **Country/ies where the study was carried out** UK **Study type** **First study:** cross–sectional primary care study. **Second study:** large national case control study. **Aim of the study** To assess the utility of proposed temperature–pulse centile charts in the clinical assessment of children with suspected serious bacterial infection (SBI). **Study dates** **First study:** Not reported. **Second Study:** December 1997 and February 1999	**Characteristics** **First study:** Age: 3 months–10 years. Gender: 786 (57.9%) Male; 574 (42.1%) Female. Diagnosis: SBI n = 55; SBI included pneumonia n= 41; sepsis without a clear focus n = 10; urinary sepsis n = 2; soft-tissue infection n = 2. **Second study:** Age: 3 months–10 years. Gender: Not reported. Diagnosis: Meningococcal septicaemia. **Inclusion criteria** **First study:** Children presenting to a paediatric presentations to a hospital emergency department in Nottingham. **Second study:** Children with meningitis. **Exclusion criteria**	detect serious illness.	collected prospectively on all children presenting to an emergency department, with the exception of children requiring emergency resuscitation directly at presentation. Methods: Each child's outcome was classified as SBI or not SBI. SBI was defined as admission to hospital plus any of the following: positive bacterial cultures from blood; radiological signs of pneumonia; clinical meningitis plus a cerebrospinal fluid polymorphonuclear leucocytosis; acute febrile purpura; deep collection(s) requiring intravenous antibiotics and or surgical drainage; a white blood cell count ≥20×10^9 /l; a C reactive protein ≥120 mg/l; or a final diagnosis of septic arthritis, osteomyelitis, empyema or mastoiditis. Children who re-attended hospital within 1 week of discharge from either the emergency department or the ward were identified from the electronic patient register, and their notes reviewed, and the final diagnoses and SBI classification amended in the light of their second presentation. **Second study:** Recruitment: Regional notification data and data from the Office for National Statistics were used to identify incident cases of paediatric meningococcal disease between	SBI were obtained. A distribution of temperature–pulse and pulse data by centile group for children presenting to the emergency department with suspected serious bacterial infection is presented below: Age specific temperature–pulse centiles, p value 0.288. **Above 97th centile:** **N children** = 132**;** **children with serious bacterial infection (n) =** 7**;** **OR =** 1.84 (95% CI 0.72 to 4.71). **Above 90th centile:** **N children** = 114**;** **children with serious bacterial infection (n)** = 4**;** **OR** = 1.19 (95% CI 0.38 to 3.73). **Above 75th centile:** **N children =** 227**;** **children with serious bacterial infection (n)** = 11**;** **OR =** 1.67 (95% CI 0.73 to 3.79). **Above 50th centile:** **N children =** 316**;** **children with serious bacterial infection (n)** = 16**;** **OR =** 1.75 (95% CI 0.83 to 3.69). **Below equal to 50th centile:** **N children =** 439**;**	Indirectness: The study includes children older than 5 years of age. **Second study:** Limitation: The main limitation of the meningococcal dataset is the inclusion of only children with meningococcal disease, therefore the researcher were unable to assess the specificity, NPV or PPV of centile cut-offs in identifying children presenting with meningococcal disease. Indirectness: The study includes children older than 5 years of age. **Other information** 1) Tachycardia was defined according to UK Advanced Paediatric Life Support (APLS) guidelines as a heart rate >160 beats/min in children less than 1 year old; more than 150 beats/min in children 1–2 years old; more than 140 beats/min in children 3–4 years old; and more than120 beats/min in children 5–12 years old. **First study:** 1) The strengths of the emergency department dataset include the large number of children for whom detailed clinical and laboratory data were collected prospectively, and the non-selective nature of the group of children included, which suggests that the findings might be generalised to other paediatric

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding One author was funded by a Wellcome Trust research training fellowship. Well Child Medical Charity funded the studies in Nottingham. The University of Oxford Department of Primary Health Care work on vital signs was founded by the NIHR programme grant 'Development and implementation of new diagnostic processes and technologies in primary care'.	**First study:** Children requiring emergency resuscitation directly at presentation. **Second study:** Children with meningitis and signs of raised intracranial pressure.		December 1997 and February 1999. Any unconfirmed cases were excluded. Methods: Each case was classified according to accepted definitions as possible, probable or confirmed meningococcal disease, following expert panel review. Severe meningococcal disease was defined a priori as a Glasgow Meningococcal Septicaemia Prognostic Score >8. Statistical analysis: The OR for SBI in each centile range was calculated, and a χ^2 test was performed. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and positive likelihood ratio (LR+) and negative likelihood ratio (LR−) were calculated and cut-offs defined by temperature–pulse centiles, pulse centiles and tachycardia alone for identifying children with SBI.	**children with serious bacterial infection (n)** = 13**;** **OR =** 1.00. **Tachycardia:** **N children =** 514**;** **children with serious bacterial infection (n)** = 34**;** **OR =** 2.90 (95% CI 1.60 to 5.26). Age specific pulse centiles, p value 0.0005. **Above 97th centile:** **N children** = 28**;** **children with serious bacterial infection (n) =** 1**;** OR = 1.51 (95% CI 0.19 to 12.0) **Above 90th centile:** **N children** = 91**;** **children with serious bacterial infection (n)** = 10**;** OR = 5.04 (95% CI 2.14 to 11.9). **Above 75th centile:** **N children =** 199**;** **children with serious bacterial infection (n)** = 12**;** OR = 2.62 (95% CI 1.19 to 5.79). **Above 50th centile:** **N children =** 324**;** **children with serious bacterial infection (n)** = 14**;** OR = 1.85 (95% CI 0.87 to 3.93). **Below equal to 50th centile:**	emergency department settings. 2) 133 (9.8%) children could not be assigned to a temperature–pulse category, because their temperature lies outside the range for which age-specific centiles have been defined. The proportion of children with SBI in this group (4 children; 3.0%) was not significantly different from those whose temperature lay within the ranges of the centile charts (p=0.523). **Second study:** 1) To investigate the utility of the temperature–pulse centile in identifying children with meningococcal septicaemia, the authors plotted these children's temperature and pulse, and performed χ^2 tests for trend in the proportion of children who had severe meningococcal disease (GSMP score >8) across centile categories. 2) Scatter graphs of admission temperature and pulse for children with and without severe disease were obtained and were superimposed on temperature–pulse centile charts obtained in the first study and no difference was observed. Higher temperature–pulse centile categories were associated with a higher proportion of children with severe disease (p=0.041 and p=0.004, respectively.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				N children = 586**;** **children with serious bacterial infection (n)** = 34**;** **OR =** 1.00. There was no significant trend across temperature–pulse centile categories in the proportion of children with SBI(p=0.288). There was strong evidence of an association between tachycardia and SBI (OR = 2.90 (95% CI 1.60 to 5.26), p=0.0002). Risk of SBI increased with higher pulse centile ranges (p=0.0005). See table below for sensitivity, specificity, PPVs and NPVs for significant bacterial infection of cut-offs defined by temperature–pulse, pulse and by tachycardia. **Age specific temperature–pulse centiles:** **Above 97th centile:** **Sensitivity (95% CI) =** 13.7 (5.7 to 26.3); **Specificity (95% CI)** = 89.4 (87.5 to 91.1); **PPV (95% CI)** = 5.3 (2.2 to 10.6); **NPV (95% CI) =** 96.0 (94.6 to 97.1); **LR^+ (95% CI)** = 1.4 (0.69 to 2.7);	3) There was no strong evidence of an association between temperature–pulse centile category and risk of SBI, reflected in the poor sensitivity, specificity, PPVs, NPVs, LR+ and LR− of individual centile cut-offs. 4) Tachycardia was defined according to UK Advanced Paediatric Life Support (APLS) guidelines as a heart rate >160 beats/min in children less than 1 year old; more than 150 beats/min in children 1–2 years old; more than 140 beats/min in children 3–4 years old; and more than120 beats/min in children 5–12 years old.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				LR– (95% CI) = 0.96 (0.48 to 1.9). **<u>Above 90th centile</u>:** **Sensitivity (95% CI) =** 21.6 (11.3 to 35.3); **Specificity (95% CI)** = 80.0 (77.6 to 82.3); **PPV (95% CI)** = 4.5 (2.3 to 7.9); **NPV (95% CI)** = 95.9 (94.5 to 97.1); **LR^+ (95% CI)** = 1.2 (0.76 to 1.8); **LR– (95% CI)** = 0.96 (0.63 to 1.5). **<u>Above 75th centile</u>:** **Sensitivity (95% CI)** = 43.1 (29.3 to 57.8); **Specificity (95% CI)** = 61.7 (58.8 to 64.5); **PPV (95% CI)** = 4.7 (2.9 to 7.0); **NPV (95% CI)** 96.2 = (94.5 to 97.4); **LR^+ (95% CI)** = 1.2 (0.58 to 2.3); **LR– (95% CI)** = 0.90 (0.45 to 1.8). **<u>Above 50th centile</u>:** **Sensitivity (95% CI)** = 74.5 (60.4 to 85.7); **Specificity (95% CI)** = 36.2 (33.4 to 39.0); **PPV (95% CI)** = 4.8 (3.4 to 6.6); **NPV (95% CI) =** 97.0 (95.0 to 98.4); **LR^+ (95% CI)** = 1.1 (0.50 to 2.6); **LR^- (95% CI)** = 0.75 (0.33 to	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				1.7). **<u>Tachycardia</u>:** **Sensitivity (95% CI)** = 66.7 (52.1 to 79.2; **Specificity (95% CI)** = 59.2 (56.3 to 62.0); **PPV (95% CI)** = 6.6 (4.6 to 9.1); **NPV (95% CI) =** 97.6 (96.2 to 98.6); **LR^+ (95% CI)** = 1.5 (0.67 to 3.4); **LR– (95% CI)** = 0.65 (0.29 to 1.46). **<u>Age specific pulse centiles:</u>** **<u>Above 97th centile</u>:** **Sensitivity (95% CI) =** 2.0 (0.04 to 10.4); **Specificity (95% CI)** = 97.7 (96.7 to 98.5); **PPV (95% CI)** = 3.6 (0.1 to18.3); **NPV (95% CI) =** 95.8 (94.5 to 96.9); **LR^+ (95% CI)** = 2.7 (2.2 to 3.4); **LR– (95% CI) =** 0.96 (0.76 to 1.2). **<u>Above 90th centile</u>:** **Sensitivity (95% CI) =** 21.6 (11.3 to 35.3); **Specificity (95% CI)** = 90.8 (89.0 to 92.4); **PPV (95% CI)** = 9.2 (4.7 to 15.9); **NPV (95% CI)** = 96.4 (95.1 to 97.4); **LR^+ (95% CI)** = 2.4 (1.6 to 3.7); **LR– (95% CI)** = 0.86 (0.57 to 1.3).	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Above 75th centile: **Sensitivity (95% CI)** = 45.1 (31.1 to 59.7); **Specificity (95% CI)** = 75.7 (73.1 to 78.1); **PPV (95% CI)** = 7.2 (4.6 to 10.7); **NPV (95% CI)** = 96.9 (95.6 to 97.9); **LR+ (95% CI)** = 1.7 (0.84 to 3.3; **LR– (95% CI)** = 0.78 (0.40 to 1.5). **Above 50th centile:** **Sensitivity (95% CI)** = 72.5 (58.3 to 84.1); **Specificity (95% CI)** = 48.6 (45.7 to 51.5); **PPV (95% CI)** = 5.8 (4.1 to 7.9); **NPV (95% CI) =** 97.6 (96.0 to 98.7); **LR^+ (95% CI)** = 1.3 (0.58 to 3.1); **LR^- (95% CI)** = 0.64 (0.28 to 1.5). (PPV positive predictive value; NPV negative predictive value; LR+ likelihood ratio of a positive test; LR– likelihood ratio of a negative test) **Second study :** The sensitivity of cut-offs defined by temperature–pulse, pulse centiles and tachycardia for detecting children with meningococcal septicaemia of various degrees of severity is	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				presented below: **Percentage sensitivity of centile ranges for identifying all children with meningococcal septicaemia and those with severe disease (95% CI)** Age-specific temperature–pulse centiles: **Above 97th centile:** **All children with meningococcal septicaemia =** 23.6 (18.5 to 29.3) **Children with severe disease on admission =** 33.3 (22.9 to 45.2). **Above 90th centile:** **All children with meningococcal septicaemia =** 37.8 (31.8 to 44.1) **Children with severe disease on admission =** 50.7 (38.9 to 62.4). **Above 75th centile:** **All children with meningococcal septicaemia =** 55.5 (49.2 to 61.7) **Children with severe disease on admission =** 62.7 (50.7 to 73.6). **Above 50th centile:** **All children with meningococcal septicaemia =** 70.1 (64.0 to 75.6) **Children with severe disease on admission** = 74.7 (63.3 to 84.0).	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Below 50th centile: **All children with meningococcal septicaemia =** 29.9 (24.4 to 36.0) **Children with severe disease on admission =** 25.3 (16.0 to 36.7). Age-specific pulse centiles: **Above 97th centile:** **All children with meningococcal septicaemia =** 11.0 (7.7 to 15.1) **Children with severe disease on admission =** 17.9 (10.2 to 28.3). **Above 90th centile:** **All children with meningococcal septicaemia =** 27.8 (22.8 to 33.2) **Children with severe disease on admission =** 38.5 (27.7 to 50.2). **Above 75th centile:** **All children with meningococcal septicaemia =** 49. (43.4 to 55.0) **Children with severe disease on admission =** 61.5 (49.8 to 72.3). **Above 50th centile:** **All children with meningococcal septicaemia =** 73.9 (68.5 to 78.8) **Children with severe disease on admission** = 84.6 (74.7 to 91.8).	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Below 50th centile: **All children with meningococcal septicaemia =** 26.1 (21.2 to 31.5) **Children with severe disease on admission =** 15.4 (8.2 to 25.3). **Tachycardia:** **All children with meningococcal septicaemia =** 68.9 (63.3 to 74.1) **Children with severe disease on admission =** 78.2 (67.4 to 86.8).	
Full citation Hanna, Colleen M., Greenes,David S., How much tachycardia in infants can be attributed to fever?, Annals of emergency medicine,Ann Emerg Med, 43, 699-705, 2004 **Ref Id** 156077 **Country/ies where the study was carried out** Emergency department Children's Hospital Boston, US. **Study type** Prospective study. **Aim of the study**	**Sample size** 490 children. **Characteristics** Age: Children younger than 1year of age. Gender: Not reported Diagnosis: Febrile state was defined as rectal temperature equal or higher of 38°C. **Inclusion criteria** Children younger than 1 year of age and presenting to a paediatric emergency department. **Exclusion criteria** Children that were fussy or crying	**Interventions** **Diagnostic evaluation** Measuring heart rate in conjunction with temperature to detect serious illness.	**Details** Recruitment: 733 children were enrolled 113 were excluded because they had one or more medical condition (other than fever) expected to cause tachycardia 170 children were excluded because they were fuss or crying 490 were includes, with a pulse rate ranging from 80 to 210 beats/min and rectal temperature ranging from 34.6 to 41.0°C. The children were divided in 6 age groups; 0-1, 2-3, 4-5, 6-7, 8-9, 10-11 months. Methods: Measurement of pulse rate and temperature were made simultaneously when the patient was first evaluated. The behavioural state of each infant was assessed during the measurement of pulse and ranked on a scale of 1 to4 as follow: 1 sleeping, 2 awake and quiet, 3	**Results** **Results** Mean pulse rate in febrile in each age group is presented below: **Age 0-1**: total n of children = 156; Afebrile children: n = 166; Mean pulse rate (95%CI) = 145 (142-148); Febrile children: n = 20; Mean pulse rate (95%CI) = 155 (150-160); Mean pulse rate difference (95%CI) = 10 (2-18). **Age 2-3**: total n of children = 85; Afebrile children: n = 78; Mean pulse rate (95%CI) = 135 (132-138); Febrile children: n = 7; Mean pulse rate (95%CI) = 152 (139-165); Mean pulse rate difference	**Limitations** Limited data on the clinical status of the patients from which to determine the exclusion criteria. Impossibility to control for baseline variation between children when evaluating the effect of temperature on pulse rate. Other limitations were in the data from patients with very low or very high temperature. At these extreme the researcher cannot be confident that the relationship between the temperature and pulse rate remains linear at this extreme temperature of the spectrum. **Other information** 1) The definition of fever in the study is temperature higher or equal to 38°C. 2) No relationship between pulse

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To evaluate if pulse rate increase linearly with increase body temperature in infant and determine how much tachycardia in infants can be explained by 1^{o}C increase in body temperature. **Study dates** July to December 2001 **Source of funding** Not reported	or if they had one or more medical condition (other than fever) expected to cause tachycardia. Such as hypovolemia, hypoxemia, cardiomyophathy, diagnosis of sepsis in the emergency department, diagnosis of serious bacterial infection, endocrine conditions, anaemia. Children with any contradiction to rectal thermometry.		fussy, 4 crying. Statistical analysis: A comparison of mean pulse rates between infants with fever and without fever was performed for age group by using the unpaired *t* test. Linear regression analysis of the relationship between pulse rate and temperature was performed for each age group. A multivariate linear regression model adjusted for age was performed. In this mode according with to a post hoc review of the data, infant in the 0-1 month age group were excluded. In the multivariate model, the dependent variable was pulse rate and the independent variables were age and rectal temperature.	(95%CI) = 17 (7-28). **Age 4-5**: total n of children = 76; Afebrile children: n = 50; Mean pulse rate (95%CI) = 131 (126-135); Febrile children: n = 26; Mean pulse rate (95%CI) = 151 (143-159); Mean pulse rate difference (95%CI) = 20 (12-29). **Age 6-7**: total n of children = 64; Afebrile children: n = 46; Mean pulse rate (95%CI) = 132 (128-135); Febrile children: n = 18; Mean pulse rate (95%CI) = 148 (139-156); Mean pulse rate difference (95%CI) = 16 (8-24). **Age8-9**: total n of children = 59; Afebrile children: n = 37; Mean pulse rate (95%CI) = 134 (127-141); Febrile children: n = 22; Mean pulse rate (95%CI) = 146 (138-153); Mean pulse rate difference (95%CI) = 12 (1-22). **Age 10-11**: total n of children = 50; Afebrile children: n = 23; Mean pulse rate (95%CI) = 129 (121-136); Febrile children: n = 27; Mean pulse rate (95%CI) = 147 (140-154);	rate and temperature was established in the 0-1 month age group, these neonates were excluded from the multivariate model. 3) The linear regression analysis showed that the pulse rate increase linearly with temperature in all age group excluded the 0-1 month group with the adjusted r^2 ranging from 0.10 to 0.38. 4) The mean increase in pulse rate per 1^{o}C increase in temperature ranged from 6.8 (95%CI, 1.8-11.7) beats/min to 10.9 (95%CI, 6.9-14.9) beats/min.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Mean pulse rate difference (95%CI) = 18 (8-28). The mean increase in pulse rate per 1°C increase in temperature: **Age 0-1** Adjusted r^2 = 0.004 Mean increase in pulse rate per 1°C increase in temperature (95%CI) = 2.2 (-1.3-5.6). **Age 2-3** Adjusted r^2 = 0.16 Mean increase in pulse rate per 1°C increase in temperature (95%CI) = 10.0 (5.1-14.8). **Age 4-5** Adjusted r^2 = 0.25 Mean increase in pulse rate per 1°C increase in temperature (95%CI) = 10.6 (6.4-14.8). **Age 6-7** Adjusted r^2 = 0.22 Mean increase in pulse rate per 1°C increase in temperature (95%CI) = 9.2 (4.9-13.4). **Age 8-9** Adjusted r^2 = 0.10 Mean increase in pulse rate per 1°C increase in temperature (95%CI) = 6.8 (1.8-11.7). **Age 10-11** Adjusted r^2 = 0.38	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Mean increase in pulse rate per 1°C increase in temperature (95%CI) = 10.9 (6.9-14.9). Multivariate linear regression analysis: Pulse rate 9.6 (95%CI 7.7-11.5) beats/min; Pulse rate adjusted for age -0.75 (95%CI 0.09- 1.41) beats/min with each additional month of life.	
Full citation Thompson,M., Coad,N., Harnden,A., Mayon-White,R., Perera,R., Mant,D, How well do vital signs identify children with serious infections in paediatric emergency care?, Archives of Disease in Childhood, 94, 888-893, 2009 **Ref Id** 177014 **Country/ies where the study was carried out** UK **Study type** Prospective cohort study **Aim of the study** To determine whether vital	**Sample size** n = 700 **Characteristics** Age: 3 months-16 years Gender: Male (53.9%) Female (46.1%) Ethnicity: White (73.1%) Asian (12.4%) **Inclusion criteria** Children aged 3 months-16 years attending the Pediatric Assessment Unit at the University Hospital Coventry and Warwickshire NHS Trust with an acute infection suspected by the	**Interventions** **Symptoms/signs** Temperature >/=39C	**Details** - All children attending the Pediatric assessment unit (PAU) were triaged by a nurse on arrival. This assessment included identifying the presenting complaint, measurement of vital signs and conscious level, together with the Manchester triage score (MTS). - The MTS system assigned children to four categories based on the maximum delay before further assessment: emergency (0 minutes), very urgent (10 minutes), urgent (60 minutes) and standard/non-urgent (120 minutes). - The triage nurses assessed activity level, respiratory distress and hydration. The vital signs measured were axillary temperature, heart rate and oxygen saturations, respiratory rate and capillary refill time. - A parental questionnaire was	**Results** Temperature >/=39C Serious infection: 33/108 Intermediate infection: 49/205 Minor infection: 48/339 No infection: 0/48 x^2: p<0.001 For predicting those with serious or intermediate infection vs. minor/no infection: Sensitivity, % (95%CI): 27 (22 to 32) Specificity, % (95%CI): 87 (84 to 91) +LR (95%CI): 2.1 (1.5 to 2.9) -LR (95%CI): 0.8 (0.8 to 0.9) Minor infection: conditions from which the child was expected to recover without sequelae Serious infection: conditions that were likely to be life threatening if untreated or with high chance of life-threatening complications or sequelae	**Limitations** Comparison of the diagnostic accuracy of vital signs with that of the NICE traffic light system was somewhat limited as the NICE system was developed for a more limited age range (0-5 years) and because data was not available on all the 'amber' and 'red' clinical features. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
signs identify children with serious infections, and to compare their diagnostic value with that of the Manchester triage score (MTS) and National Institute for Health and Clinical Excellence (NICE) traffic light system of clinical risk factors. **Study dates** Not reported **Source of funding** Funded by the Medical Research Council as part of a programme grant in childhood infection in primary care. Researchers were independent from the funders of the study.	parents, referring clinician or triage nurse. **Exclusion criteria** Children with diseases liable to cause repeated serious bacterial infection (including haematological malignancies, iatrogenic immunosuppression), and infections resulting from penetrating trauma.		completed on arrival at the PAU which included a check list of 22 presenting symptoms. The children's clinical features of colour, activity, level, respiratory effort, hydration, presence of neck stiffness and non-blanching rash, as well as vital signs were categorised, blind to final outcome, into the NICE traffic light classification of intermediate (amber) and high (red) risk categories. - Details of hospital admissions were obtained from the hospital medical records. For children who were either not admitted or admitted for less than 24 hours, the PAU records were looked at for evidence of another visit in the next 7 days. - A 'severity of infection' reference standard was created based on the final diagnosis made by senior paediatricians at the time of discharge from the PAU, or inpatient ward if the child was admitted. The final diagnosis was categorised by the severity of infection: 1) minor infection 2) serious infection 3) intermediate infection 4) not infection group - Associations between vital signs with severity of infection were tested using x^2 tests. Fever was defined as >/=39C. - The combination of vital signs that provided optimum discrimination between serious and minor infection were determined. The diagnostic	Intermediate infection: Conditions that were not likely to be life-threatening, but were expected to last for > 10 days or have a non-life-threatening complication No infection: Final diagnosis that was not an acute infection	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			characteristics of the MTS were dichotomised as 1) standard vs. urgent/very urgent/emergency and 2) standard/urgent vs. very urgent/emergency		

Chapter 8

Children 3 months and older

Review question

What is the predictive value of procalcitonin compared to C-reactive protein for detecting serious illness in fever without apparent source in children under 5?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Lacour,A.G., Gervaix,A., Zamora,S.A., Vadas,L., Lombard,P.R., Dayer,J.M., Suter,S., Procalcitonin, IL-6, IL-8, IL-1 receptor antagonist and C-reactive protein as identificators of serious bacterial infections in children with fever without localising signs, European Journal of Pediatrics, 160, 95-100, 2001 **Ref Id** 83852 **Country/ies where the study was carried out** Switzerland **Study type** Prospective cohort study **Aim of the study** To investigate whether the determination, in addition to the previously used parameters, of PCT, IL-6, IL-8 or IL-1 Ra offered an	**Sample size** N = 124 analysed; 133 included and 9 excluded. **Characteristics** Age = 7 to 36 months **Inclusion Criteria** Not reported **Exclusion Criteria** 1. Children with fever lasting longer than 7 days. 2. Neonates of less than 1 week and 3. All children treated with antibiotics during the 2 previous days as well as those with known immunodeficiences (like neutropenia due to chemotherapy or HIV-infected children).	**Tests** **Index test** 1. PCT 2. CRP 3. IL-6 4. IL-8 5. Il-1Ra 6. Leucocytes 7. Band count 8. McCarthy score 9. PCT or CRP 10. PCT or Leucocytes **Reference test** 1. Bacteremia - blood culture 2. Pyelonephritis - urine culture 3. DMSA renal scintigraphy 4. Chest X-ray 5. CSF culture	**Methods** Recruitment: Children aged 7 to 36 months of age consulting the Emergency Department of the University Children's Hospital of Geneva with a rectal temperature above 38^{o}C and without localising signs of infection in their history or at physical examination were prospectively enrolled. After examination by paediatric resident, the children were tested They also had a clinical follow-up with physical examination by a paediatrician within the following 48h or by telephone contact. The diagnosis was registered at the end of the clinical follow-up. Infections requiring intravenous antibiotic therapy such as bacteremia, pyelonephritis, lobar pneumonia, meningitis or osteoarthritis were defined as SBI. The remaining patients suffered from infections classified as benign for the purpose of the study on the basis that they did neither require oral antibiotic therapy at follow-up nor parenteral therapy for infections such as acute otitis media, lower UTI, gastroenteritis or adenitis.	**Results** SBI prevalence = 22.6% Bacteremia - 4 Pyelonephritis - 19 Lobar pulmonary condensation - 5 <u>PCT - 0.9 ng/ml</u> Sensitivity = 93 (77 to 99) Specificity = 78 (69 to 86) *PPV = 55 (41 to 70) *NPV = 97 (94 to 101) **+LR = 4.2 (2.9 to 6.3) **-LR = 0.1 (0.0 to 0.3) <u>CRP - 40 mg/l</u> Sensitivity = 89 (72 to 98) Specificity = 75 (65 to 83) *PPV = 96 (92 to 100) *NPV = 51 (37 to 65) **LR+ = 3.6 (2.5 to 5.2) **LR- = 0.1 (0.0 to 0.4)	**Limitations** 1. It is not clear whether there was blinding in interpreting all reference (except the chest x-ray) and or index tests. **Other information** 1. Among the 28 children with SBI, 2 had a PCT concentration below the cut-off level (0.9 ng/ml) 2. Authors' conclusion on PCT vs. CRP: "On the basis of our data, PCT offers only a modest advantage over CRP, which at present is more easily measurable in an outpatient setting".

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
advantage in terms of sensitivity and specificity, with which a SBI could be predicted. **Study dates** March 1998 to August 1999 **Source of funding** Not reported				**Combined tests** PCT (0.9ng/ml) or CRP (40mg/l) Sensitivity = 96 (82 to 100) Specificity = 67 (56 to 76) *PPV = 46 (33 to 58) *NPV = 98 (95 to 101) **LR+ = 2.9 (2.2 to 3.9) **LR- = 0.1 (0.0 to 0.4) **Results by age** PCT 0.9 ng/ml: <12 months (n = 80) Sensitivity = 94 (Not reported) Specificity = 87 (Not reported) PPV = 68 (Not reported) NPV = 98 (Not reported) LR+ = Not reported LR- = Not reported >12 months (n=44) Sensitivity = 90 (Not reported) Specificity = 62 (Not reported) PPV = 41 (Not reported) NPV = 96 (Not reported) LR+ = Not reported LR- = Not reported CRP 40 mg/l: <12 months (n = 80)	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Sensitivity = 94 (Not reported) Specificity = 84 (Not reported) PPV = 63 (Not reported) NPV = 98 (Not reported) LR+ = Not reported LR- = Not reported <u>>12 months (n = 44)</u> Sensitivity = 80 (Not reported) Specificity = 59 (Not reported) PPV = 91 (Not reported) NPV = 36 (Not reported) LR+ = Not reported LR- = Not reported *Confidence intervals calculated by the NCC technical team ** Results calculated by the NCC technical team	
Full citation Pratt,A., Attia,M.W., Duration of fever and markers of serious bacterial infection in young febrile children, Pediatrics International, 49, 31-35, 2007 **Ref Id**	**Sample size** n = 119 children (included); 128 children enrolled and 9 children excluded **Characteristics** Median age (range) = 10 (1 to 34) months	**Tests** **Index test** 1. CRP 2. White blood cell count (WBC) 3. Absolute neutrophil count (ANC) **Reference test**	**Methods** Recruitment: A sample of children who presented to the duPont Hospital for Children Emergency Department with reported or documented fever ≥ 39^{o}C who fulfilled the inclusion criteria were enrolled. Intervention: All patients had a complete blood count, blood culture and CRP level drawn. A	**Results** <u>SBI ≤12h</u> Prevalence = 6/45 (13.3%) UTI = 5 cases Bacteremia = 1 case **CRP (3mg/dL)** Sensitivity = 67 (24 to 94) Specificity = 74 (58	**Limitations** 1. Not all the participants had a chest X-ray: "Chest X-ray was performed at the discretion of the treating physician". **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
84029 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** To evaluate C-reactive protein (CRP) as a predictor of serious bacterial infection SBI with respect to duration of fever, specifically ≤12h of fever or >12h. **Study dates** January 2002 to July 2003 **Source of funding** Not reported	**Inclusion Criteria** Children who after careful history and physical exam by housestaff and attending paediatric emergency medicine physicians were found to have no localizing source of fever, were eligible to be enrolled in the study. **Exclusion Criteria** 1. Children who had an explainable cause of fever such as acute otitis media, acute pharyngitis, acute respiratory tract infection, acute grastroenteritis and those who had a positive viral study were excluded. 2. Those with a history of antibiotic use during the past 10 days, a known underlying immunologic disease, or vaccination during the previous 2 days were also excluded.	1. Occult bacteremia - blood culture 2. UTI - urinalysis 3. Pneumonia - Chest X-ray	urinalysis and/or urine culture was obtained by bladder catheterisation on patients under 6 months of age as per current standards of care. A chest X-ray was performed at the discretion of the treating physician. Serious bacterial infections were based on laboratory or radiographic results (bacteremia, meningitis, urinary tract infection, pneumonia, septic arthritis, and osteomyelitis). WBC was quantified using quantified using automated laboratory equipment. Laboratory personnel calculated the differential WBC count using microscopy. Blood cultures were monitored using the Isolator Blood culture System. Quantitative CRP concentration was obtained using particle-enhanced turbidometric immunoassay technique. Laboratory personnel and radiology staff were blinded to clinical information. Statistical analysis: Sample size was estimated considering that the most sensitive bacterial marker is CRP. The study was adequately powered.	to 86) LR+ = 2.6 (1 to 5.2) LR- = 0.4 (0.1 to 1.4)* PPV = 28 (5 to 52)* NPV = 94 (85 to 102)* **5mg/dL** Sensitivity = 50 (14 to 86) Specificity = 92 (78 to 98) LR+ = 6.5 (1.7 to 22.3) LR- = 0.5 (0.2 to 1.2)* PPV = 50 (10 to 90)* NPV = 92 (84 to 101)* **7mg/dL** Sensitivity = 33 (6 to 76) Specificity = 97 (85 to 100) LR+ = 13 (1.8 to 88.4) LR- = 0.7 (0.4 to 1.2)* PPV = 67 (13 to 120)* NPV = 90 (82 to 99)* <u>SBI >12h</u> Prevalence = 11/74 (14.9%) UTI = 8 cases Pneumonia = 3	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				cases **CRP (3mg/dL)** Sensitivity = 100 (72 to 100) Specificity = 63 (50 to 75) LR+ = 2.7 (1.7 to 3.8) LR- = 0.0 (0.0 to 6.8)* PPV = 32 (17 to 48)* NPV = 100 (98 to 101)* **5mg/dL** Sensitivity = 82 (48 to 97) Specificity = 79 (67 to 88) LR+ = 4 (2.1 to 6.9) LR- = 0.2 (0.1 to 0.8)* PPV = 41 (20 to 61)* NPV = 96 (91 to 101)* **7mg/dL** Sensitivity = 73 (40 to 93) Specificity = 81 (69 to 89) LR+ = 3.8 (1.9 to 7) LR- = 0.3 (0.1 to 0.9)* PPV = 40 (19 to 61)* NPV = 94 (88 to 101)* *Calculated by the NCC technical team	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Galetto-Lacour,A., Zamora,S.A., Gervaix,A., Bedside procalcitonin and C-reactive protein tests in children with fever without localizing signs of infection seen in a referral center, Pediatrics, 112, 1054-1060, 2003 **Ref Id** 93988 **Country/ies where the study was carried out** Switzerland **Study type** Prospective cohort study **Aim of the study** To assess the value of bedside tests for predicting the occurrence of severe bacterial infections (SBI) in children with fever without source **Study dates** Not reported **Source of funding** Not reported	**Sample size** n = 99 children (analysed); n = 110 children enrolled and 11 children excluded **Characteristics** Age = 7days to 36 months **Inclusion Criteria** Children that had a rectal temperature ≥38^{o}C and no localising signs of infection in their history or at physical examination **Exclusion Criteria** Children with fever lasting longer than 7 days, children who were treated with antibiotics during the 2 previous days, and those with known immunodeficiencies.	**Tests** **Index test** 1) Procalcitonin (PCT) 2) C-reactive protein (CRP) 3) Leukocytes 4) Band 5) IL-6 6) YOS score **Reference test** 1) Bacteremia - blood culture; 2) Pyelonephritis - Urine culture and 99M-dimercaptosuccinic acid (DMSA) renal scintigraphy; 3) Lobar pneumonia - chest radiograph; 4) Bacterial meningitis - CSF culture; 5) Deep abscess - computed tomography scan and surgical exploration.	**Methods** Recruitment: In the ED of the University Children's Hospital of Geneva, the investigators prospectively enrolled children, aged 7 days to 36 months, who had a rectal temperature 38°C and no localizing signs of infection in their history or at physical examination. Intervention and methods: Children were examined by a paediatric resident who took a complete history, performed a physical examination, recorded the degree and duration of fever, and determined a clinical score, according to McCarthy. All children had a WBC count with differential and a determination of CRP, PCT, and IL-6 values. Toxic-appearing children had a full sepsis workup, were admitted to the hospital, and were given parenteral antibiotics. Nontoxic-appearing children, from 1 week to 90 days of age or from 91 days to 36 months of age with fever 39°C, had a urine collection by suprapubic aspiration, transurethral bladder catheterization, or midstream catch for analysis and culture. Blood was systematically cultured in children with leukocytes 15 g/L or band counts 1.5 g/L. In children from 91 days to 36 months of age with fever 38°C but 39°C, urine and blood culture were not performed unless biological risk	**Results** SBI Prevalence = 29/99 (29%) Occult bacteremia - 4 cases Pyelonephritis - 21 cases Lobar pneumonia - 2 cases Mastoiditis - 1 case Retropharyngeal abscess - 1 **PCT (0.5 ng/mL)** Sensitivity = 93 (77 to 99) Specificity = 74 (62 to 84) LR+ = 3.6 (2.4 to 5.5)* LR- = 0.09 (0.02 to 0.36) NPV = 96 (91 to 101)* PPV = 60 (46 to 74)* Post-test probability = 3% **CRP (40 mg/L)** Sensitivity = 79 (65 to 94) Specificity = 79 (69 to 88) LR+ = 3.7 (2.3 to 6.0)* LR- = 0.26 (0.13 to 0.54) PPV = 61 (45 to 76)* NPV = 90 (83 to 98)* Post-test probability	**Limitations** 1. Participants did not receive the same reference standard, nontoxic-appearing children received individualised tests according to clinical and laboratory criteria/results. **Other information** 1. Children were classified as having a benign infection for the purpose of this study on the basis of: i) **negativity of blood or CSF culture**, ii) **positive urine culture with a normal DMSA renal scintigraphy**, iii) **clinical improvement** without antibiotics, and iv) the presence of a **focal infection at the follow-up visit** such as otitis media or gastroenteritis. 2. Blood culture was performed in 88 (89%) children, a urine culture in 89 (90%), and a CSF culture in 17 (17%). Of 40 (40%) children who were hospitalized, 35 (88%) were treated with antibiotics, only by intravenous route, and among those sent home, antibiotics were prescribed for 36 (61%; 10 oral, 1 intramuscularly, and 25 intravenously). 3. **Authors conclusion**: "Comparing the 3 rapid tests, PCT seems to have a slight advantage over CRP because of its earlier increase after stimulation and a better negative predictive value. Nonetheless, although this test seems promising, it has been investigated less than CRP in children and needs additional investigation."

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			factors (leukocytes 15 g/L, band counts 1.5 g/L, or leukocyturia) were present. A spinal tap was performed when meningitis was suspected. Results of both assays were read by 2 investigators (A.L.G., A.G.) in a blinded manner, and the similarity of results was 99%. Decisions on antibiotic treatment and hospitalization were made by the resident in charge of the patient, based on clinical assessment and the presence of biological risk factors. All children had a clinical follow-up with physical examination by a paediatrician in the following 48 hours or by telephone contact. Antibiotics were discontinued after 48 to 72 hours if the results of the cultures were negative. The diagnosis was registered at the end of the clinical follow-up. Children were examined by a paediatric resident who took a complete history, performed a physical examination, recorded the degree and duration of fever, and determined a clinical score, according to McCarthy	= 10% *Calculated by the NCC technical team	culture in 89 (90%), and a CSF Culture in 17 (17%). Of 40 (40%) children who were hospitalized, 35 (88%) were treated with antibiotics, only by intravenous route, and among those sent home, antibiotics were prescribed for 36 (61%; 10 oral, 1 intramuscularly, and 25 intravenously).

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Andreola,B., Bressan,S., Callegaro,S., Liverani,A., Plebani,M., Da,Dalt L., Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department, Pediatric Infectious Disease Journal, 26, 672-677, 2007 **Ref Id** 119252 **Country/ies where the study was carried out** Italy **Study type** Prospective cohort study **Aim of the study** To determine the diagnostic performance of PCT and CRP, in comparison to that of WBC and ANC, in detection of serious bacterial infection (SBI) in paediatric patients admitted to the Paediatric Emergency Department	**Sample size** n = 408 children analysed; n = 435 enrolled and 27 excluded. **Characteristics** Age = 2 to 20 months **Inclusion Criteria** 1. All infants aged 7-days to 3-months old with fever >38^{o}C 2. Children aged 3 to 36 months old ill/toxic-appearing or with fever >39.5^{o}C. **Exclusion Criteria** 1. Antibiotic use within the 48 hours before admission to the hospital. 2. Vaccination during the previous 2 days. 3. Known immunodeficiencies. 4. Any chronic pathology. 5. Fever lasting longer than 5 days.	**Tests** **Index test** 1. CRP 2. PCT 3. WBC 4. ANC **Reference test** (1) bacteremia— blood culture (2) acute pyelonephritis— urine culture and DMSA scan; (3) lobar pneumonia— chest radiograph (4) bacterial meningitis— cerebrospinal fluid culture; (5) bone or joint infections— blood culture (6) sepsis - defined according to Levy et al 2003 (1) bacteremia—recovery of a single bacterial pathogen using standard culture techniques; (2) acute pyelonephritis— growth of a single urinary tract pathogen at 105 colony-forming units/mL in 2 consecutive urine samples and presence of a renal hypocaptation at DMSA scan performed within the first week after admission;	**Methods** Recruitment: The study was conducted in the tertiary care emergency department of the children's hospital in Padova. The study included all children younger than 3 years who were consecutively admitted to the Emergency Department with fever of uncertain, who, after careful history and physical examination, underwent blood analysis because more likely to have a serious bacterial infection. Intervention: According to the guidelines in use at the time of the study in the Department, in all patients the WBC, ANC, and quantitative CRP concentration were, along with urine analysis, obtained; in addition, a serum sample was also collected and stored at -20^{o}C for later determination of PCT level. Toxic appearing children had a full sepsis workup. Infants from 1-week to 90-days of age and children ill-appearing aged 3 to 36 months received a blood culture and 2 consecutive urine cultures. Urine was collected and in the presence of growth of a single urinary tract pathogen in 2 consecutive urine samples, 99mTc-dimercaptosuccinic acid (DMSA) scintigraphy was performed. Chest radiograph as well as other laboratory and radiographic tests were conducted at the discretion of the child's physician. The X-ray results were	**Results** Serious bacterial infections = 94/408 (23%) Pyelonephritis - 50 Pneumonia - 24 Meningitis - 7 Occult bacteremia - 6 Sepsis - 3 Osteomyelitis - 2 Septic arthritis - 2 **PCT 0.5 ng/mL** Sensitivity = 73.4 (63.3 to 82.0) Specificity = 76.4 (71.3 to 81.0) *PPV = 48 (40 to 56) *NPV = 91 (87 to 94) **LR+ = 3.10 (2.5 to 3.9) **LR- = 0.35 (0.2 to 0.5) 1 ng/mL Sensitivity = 63.8 (53.3 to 73.5) Specificity = 89.8 (85.9 to 92.9) *PPV = 65 (55 to 75) *NPV = 89 (85 to 93) **LR+ = 6.24 (4.4 to 9.0) **LR- = 0.40 (0.3 to 0.5) 2 ng/mL Sensitivity = 47.9	**Limitations** 1. Indirectness of population: Toxic appearing children were included in the study. 2. All participants did not receive the same reference standard. Toxic appearing children were given a full sepsis work up while well appearing children were given tests if the fulfilled certain criteria. 3. Apart from the chest X-ray, it is not clear whether any other test (reference or index) was interpreted in a blinded manner. **Other information** 1. There was no significant difference when AUCs of PCT and CRP were compared (p = 0.748) 2. Subgroup analysis by age found no difference in the AUC for both PCT and CRP between infants aged <3 months and children aged 3 to 36 months respectively. In children with evolution of fever earlier than 8 hours before admission (n = 45), PCT presented a better diagnostic performance than did CRP but this was not statistically significant (p = 0.056). 3. Authors conclusion: CRP and PCT are both valuable markers for prediction of SBI in children admitted to an Emergency department with fever without source. PCT seems to be a more accurate predictor at the beginning of an infection whereas CRP, if correctly employed may be a better test in emergency settings because of its overall better sensitivity and feasibility.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
for fever without a source. **Study dates** May 1, 2004 and Octover 31, 2005 **Source of funding** Not reported		(3) lobar pneumonia—presence of focal infiltrate on chest radiograph observed by the paediatric radiologist in a blinded manner; (4) bacterial meningitis—positive cerebrospinal fluid culture; (5) bone or joint infections—local isolation or isolation in blood culture of a microorganism; and (6) sepsis defined according to Levy et al19	observed by the paediatric radiologist in a blinded manner. A spinal tap was performed when meningitis was suspected. Erythrocyte, platelet, and WBC were performed in blood samples mixed with ethylenediaminetetraacetic acid using an automated cell counter. CRP values were determined employing a nephelometric assay, according to the instructions of the manufacturer. Quantitative measurements of PCT concentrations were performed using a sandwich immunoluminometric method, employing 2 monoclonal antibodies: one against the catacalcin region of procalcitonin and the other against calcitonin.	(37.5–58.4) Specificity = 96.5 (93.8 –98.2) *PPV = 80 (70 to 91) *NPV = 86 (82 to 90) **LR+ = 13.62 (7.4 to 25.3) **LR- = 0.54 (0.4 to 0.7) **CRP 20 mg/L** Sensitivity = 88.3 (80.0 to 94.0) Specificity = 60.8 (55.2 to 66.3) *PPV = 40 (34 to 47) *NPV = 95 (91 to 98) **LR+ = 2.25 (1.9 to 2.6) **LR- = 0.19 (0.1 to 0.3) 40 mg/L Sensitivity = 71.3 (61.0 to 80.1) Specificity = 81.2 (76.4 to 85.4) *PPV = 53 (44 to 62) *NPV = 90 (87 to 94) **LR+ = 3.79 (2.9 to 4.9) **LR- = 0.35 (0.3 to 0.5) 80 mg/L Sensitivity = 46.0 (36.4 to 57.4) Specificity = 94.6 (91.5 to 96.8) *PPV = 72 (60 to 83) *NPV = 85 (82 to 89)	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				LR+ = 8.65 (5.1 to 14.1) **LR- = 0.56 (0.5 to 0.7) **Duration of fever before admission Fever earlier than 8hours (n = 45) PCT - 1 ng/ml Sensitivity = 85.7% Specificity = 100%; 95% Confidence intervals not reported *Results calculated by the NCC technical team ** Confidence intervals calculated by the NCC technical team	
Full citation Maniaci,V., Dauber,A., Weiss,S., Nylen,E., Becker,K.L., Bachur,R., Procalcitonin in young febrile infants for the detection of serious bacterial infections, Pediatrics, 122, 701-710, 2008 **Ref Id** 119334 **Country/ies where the**	**Sample size** n = 234 included; n = 874 children enrolled and 640 children excluded **Characteristics** Age = ≤ 3 months **Inclusion Criteria** Infants of all gestational ages	**Tests** **Index test** 1. Procalcitonin 2. ANC 3. WBC **Reference test** (1) bacteremia - positive blood culture (2) UTI - urine culture or urinalysis (3) bacterial meningitis - Positive CSF culture (4) bacterial pneumonia -	**Methods** Recruitment: Infants with measured temperature of ≥38.0°C who were seen in the ED were eligible for enrolment. Intervention: All subjects received clinical care as determined by the treating paediatric emergency medicine physician. Institutional guidelines for the care of febrile infants ≤90 days of age included a complete blood count with differential, blood culture, uringalysis and urine culture with samples collected through bladder catherization, CSF cell count,	**Results** a cut-off value of 0.13 ng/mL yielded sensitivity of 96.7% (95% CI: 81.0%–99.8%), specificity of 30.3% (95% CI: 24.0%–37.5%), NPV of 98.3% (95% CI: 89.7%–99.9%), and negative likelihood ratio of 0.11	**Limitations** 1. Participants received tests depending on what condition was suggested by physical examination or clinical history. **Other information** Procalcitonin levels could not be determined for the other 201 subjects because a blood sample was not sent from the ED (n 5), the remaining blood sample could not be located in the laboratory storage refrigerator (n 25), or the remaining sample was either too hemolyzed or of insufficient quantity for accurate measurement of procalcitonin (n

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
study was carried out USA **Study type** Prospective cohort study **Aim of the study** The objectives of the study were: 1, To study the test performance of procalcitonin for identifying serious bacterial infections in febrile infants ≤90 days of age without an identifiable bacterial source and to determine an optimal cutoff value to identify infants at low risk for serious bacterial infections. **Study dates** October 2005 to March 2007. **Source of funding** Financial support from Frederick H. Lovejoy, Jr, MD, Resident Research Fund and an American Academy of Paediatrics resident research grant.	**Exclusion Criteria** Infants with previously identified immunodeficiency or chronic disease, focal bacterial infection on physical examination, vesicoureteral reflux requiring antibiotic prophylaxis, surgery in the previous 7 days, immunisations in the 48 hours preceding the visit, or antibiotic treatment within the previous 48 hours were excluded	positive pleural fluid culture result or a chest radiograph with a positive blood or sputum culture result with a respiratory pathogen; or (5) bacterial gastroenteritis - stool culture.	protein level, and glucose level analyses, gram-staining, and culture, chest radiograph if pneumonia was suggested by physical examination, and stool faecal leukocyte count and culture if clinical history or physical examination suggested possible bacterial gastroenteritis. To ensure identification of all potentially eligible febrile infants and to assess a capture rate for the study, an electronic log of ED visits was reviewed daily. The medical record was reviewed to identify potentially missed cases. Infants' caregivers who had not been approached for consent during the ED visit were called by the treating ED physician and offered enrolment in the study. Definite SBIs were: Bacteremia, UTI, meningitis, pneumonia, and gastroenteritis. Procalcitonin was measured at a reference laboratory by using an immunometric assay with time-resolved amplified crypate emission technology. The concentration of procalcitonin is calculated from an internal procalcitonin standard curve. Methodology: The laboratory investigators were blinded to the identity of all clinical information about the subjects. The final classification (definite SBI, possible SBI, or no SBI) was determined through consensus review by the 4 authors based at the primary study site, before	(95% CI: 0.02–0.76) <u>Definite SBI = 30/234 (13%)</u> Bacteremia - 4 UTI - 24 Bacteremia/UTI - 2 **PCT 0.13 ng/mL** Sensitivity = 96.7% (81.0% to 99.8%) Specificity = 30.3% (24.0% to 37.5%), PPV = 17% (11% to 23%)* NPV = 98.3% (89.7% to 99.9%), LR+ = 1.4 (1.2 to 1.6)* LR- = 0.11 (0.02 to 0.76) <u>Definite possible SBI = 42/234 (18%)</u> Definite: UTI - 7, Bacterial pneumonia - **PCT 0.12 ng/mL** Sensitivity = 95.2% (83% to 99%), Specificity = 25.5% (20% to 32%), PPV = 22% (16% to 28%)* NPV = 96.1% (85.4% to 99.3%) LR+ = 1.3 (1.1 to 1.4)* LR- = 0.19 (0.05 to 0.74).	171)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			knowledge of the procalcitonin result.	*Calculated by the NCC technical team	
Full citation Olaciregui,I., Hernandez,U., Munoz,J.A., Emparanza,J.I., Landa,J.J., Markers that predict serious bacterial infection in infants under 3 months of age presenting with fever of unknown origin, Archives of Disease in Childhood, 94, 501-505, 2009 **Ref Id** 119349 **Country/ies where the study was carried out** Spain **Study type** Retrospective cohort study **Aim of the study** To evaluate potential markers of serious bacterial infection (SBI) in infants under 3 months of age presenting with fever of unknown origin.	**Sample size** n = 347 children **Characteristics** Age = 4 to 90 days Mean duration of fever = 15 hours **Inclusion Criteria** Not reported **Exclusion Criteria** Lack of blood test, fever of more than 7 days' duration, antibiotic therapy in the 48 h prior to diagnosis, and the presence of any type of immunodeficiency.	**Tests** **Index test** 1) Procalcitonin (PCT) 2) C-reactive protein (CRP) 3) Leucocyte count 4) Neutrophil count **Reference test** (1) Microbiologically confirmed bacteraemia (2) Bacterial meningitis - cerebrospinal fluid (CSF) culture; (3) Sepsis, established according to the criteria defined by **Levy et al** including documented or suspected infection and findings of inflammation such as haemodynamic instability, tissue perfusion alteration and indications of organ dysfunction; (4) Urinary tract infection - urine culture (5) Pneumonia - chest x ray; (6) Bacterial gastroenteritis - Stool culture (7) Cellulitis - physical examination.	**Methods** Recruitment: The study included all consecutive infants between 4 and 90 days of age seen in the emergency department for fever (rectal temperature .38uC), in whom a detailed history and physical examination did not reveal a focus of infection, and in whom a blood test was performed. The study was performed in the paediatric emergency department of Donostia Hospital (San Sebastian, Spain) between January 2004 and December 2006. Intervention: Demographic, personal, clinical (degree and duration of fever), physical examination, and laboratory (leucocyte count, neutrophils, CRP, and semi-quantitative PCT; PCT-Q) data were recorded. Two subgroups of infants were defined according to duration of fever greater or less than 12 h.	**Results** SBI prevalence = 82/347 (23.6%) UTI = 69 (4 with bacteraemia), Occult bacteraemia = 5 Cellulitis = 2 (1 with bacteraemia) Sepsis = 4 (2 with bacteraemia) Acute bacterial gastroenteritis = 1 (with bacteraemia), Pneumonia = 1 CRP (mg/l) >20 64 (54 to 74) 84 (80 to 88) 55 (45 to 65) 88 (84 to 92) 4 0.43 >30 59 (48 to 70) 89 (85 to 93) 63 (52 to 74) 87 (83 to 91) 5.4 0.46 c PCT-Q (ng/ml) >0.5 63 (52 to 74) 87 (83 to 91) 59 (48 to 70) 89 (85 to 93) 4.8 0.42 **CRP (≥20 mg/l)** Sensitivity = 64 (54 to 74)	**Limitations** Retrospective study design. **Other information** 1. All the participants did not undergo all the tests - Blood cultures were obtained in 330 (95%) patients, urine cultures in 333 (96%), CSF cultures in 170 (49%), leucocyte and neutrophil counts in 342 (99%), CRP in 339 (98%), and PCT in 320 (92%). 2. Twenty-eight patients were excluded (the attending doctor chose not to perform a blood test in 25 and three had received antibiotic therapy in 48hours prior to diagnosis). Only 7.5% of the infants were excluded, due mainly to the fact that the good general state of these infants led the doctor to consider blood tests unnecessary. that the good general state of these infants led the doctor to consider blood tests unnecessary

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates January 2004 to December 2006 **Source of funding** Not reported				Specificity = 84 (80 to 88) PPV = 55 (45 to 65) NPV = 88 (84 to 92) *LR+ = 4 (2.9 to 5.5) *LR- = 0.43 (0.3 to 0.6) **CRP (≥30 mg/l)** Sensitivity = 59 (48 to 70) Specificity = 89 (85 to 93) PPV = 63 (52 to 74) NPV = 87 (83 to 91) *LR+ = 5.4 (3.6 to 7.9) *LR- = 0.46 (0.4 to 0.6) **PCT-Q (≥0.5 ng/ml)** Sensitivity = 63 (52 to 74) Specificity = 87 (83 to 91) PPV = 59 (48 to 70) NPV = 89 (85 to 93) *LR+ = 4.8 (3.5 to 7.0) *LR- = 0.42 (0.3 to 0.6) <u>Bacteraemia/Sepsis</u> Bacteraemia/Sepsis prevalence = Not reported **CRP (>30 mg/l)** Sensitivity = 56 (32	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				to 80) Specificity = 74 (69 to 79) PPV = 9.6 (4 to 16) NPV = 97 (95 to 99) LR+ = 2.15 LR- = 0.59 **PCT-Q (>0.5 ng/ml)** Sensitivity = 86 (58 to 100) Specificity = 93 (90 to 96) PPV = 35 (19 to 51) NPV = 99 (98 to 100) LR+ = 12.3 LR- = 0.15 *confidence intervals calculated by the NCC technical team	
Full citation Thayyil,S., Shenoy,M., Hamaluba,M., Gupta,A., Frater,J., Verber,I.G., Is procalcitonin useful in early diagnosis of serious bacterial infections in children?, Acta Paediatrica, 94, 155-158, 2005 **Ref Id** 119373 **Country/ies where the**	**Sample size** N = 72 children (included = 86 children; excluded = 14 children) **Characteristics** Median (range) age = 18.5 (1 to 36) months. Median duration (range) of febrile illness = 2 (1 to 8) days. **Inclusion Criteria**	**Tests** **Index test** 1. Procalcitonin 2. C-reactive protein 3. WBC 4. Combination-PCT+CRP+WBC 5. McCarthy score **Reference test** 1. Blood culture 2. Chest X-ray 3. Urine culture 4. CSF culture	**Methods** Recruitment and setting: The investigators enrolled children with fever without localizing signs (>39^{o}C) who were attending the paediatric directorate at two university hospitals within the study period. Test: All the children had full blood count, CRP, PCT, blood cultures, chest X-ray, urine culture and a clinically scoring at admission. Selected cases had cerebrospinal fluid examination, PCR, throat swab and nasopharyngeal aspirate. The	**Results** SBI = 8/72 (11.1%) Bacterial pneumonia = 1 Meningitis = 2 Septicaemia = 3 Acute pyelonephritis = 2 CRP >50mg/l*: Sensitivity = 75 (45 to 105) Specificity = 69 (57 to 80) PPV = 23 (7 to 39) NPV = 96 (90 to	**Limitations** 1. The execution of the reference standard was not described in sufficient detail. 2. It is not clear whether the index test results were interpreted without knowledge of the results of the index test 3. Blood cultures (gold standard) in the study population was done only when other markers of infection were positive which could have introduced bias into the analysis **Other information** 1. Possible bacterial Infection = 19/72 (26.4%) Viral infection = 7/72 (9.7%)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
study was carried out UK **Study type** Prospective cohort study **Aim of the study** To compare diagnostic accuracy of procalcitonin for early diagnosis of serious bacterial infection (SBI) in children presenting with fever and no focus of infection. **Study dates** January 2003 to September 2003. **Source of funding** North Tees and Hartlepool R&D Department funded the study.	Not reported. **Exclusion Criteria** 1. They excluded children who had taken antibiotics in the past 72 hours 2. Immune deficient children. 3. Children who had fever for more than 7 days.		isolation of the pathogenic organism from a normally sterile body fluid/tissue was considered as the gold standard for diagnosing serious bacterial infection. Children were classified into one of the three categories depending on the clinical and laboratory data, serious bacterial infection (SBI), possible bacterial infection (no pathogenic organism isolated; however, child received antibiotics for 24 to 48 h, until culture results available), viral or possible viral infection (isolation of virus and/or uneventful recovery without antibiotics) Statistical analysis: The study was adequately powered.	102) LR+ = 2.4 (1.4 to 4.1) LR- = 0.4 (0.1 to 1.2) PCT >0.5 ng/l*: Sensitivity = 88 (65 to 110) Specificity = 50 (38 to 62) PPV = 18 (6 to 30) NPV = 97 (91 to 103) LR+ = 1.8 (1.2 to 2.5) LR- = 0.3 (0.0 to 1.6) PCT >2 ng/l*: Sensitivity = 50 (15 to 85) Specificity = 86 (77 to 94) PPV = 31 (6 to 56) NPV = 93 (87 to 100) LR+ = 3.6 (1.4 to 8.9) LR- = 0.6 (0.3 to 1.2) *All confidence intervals calculated by the NCC technical team	Possible viral infection = 38/72 (52.8%) 2. Authors conclusion: While elevation of all the inflammatory markers makes SBI very likely in fever without localising signs (FWLS), normal procalcitonin (or any other markers studied) does not exclude SBI in this population
Full citation Gomez,B., Mintegi,S., Benito,J., Egireun,A., Garcia,D., Astobiza,E., Blood culture and	**Sample size** n = 1018 children **Characteristics**	**Tests** **Index test** 1. CRP 2. WBC	**Methods** Recruitment: Data were extracted from our registry of infants with FWS younger than 3 months old. Infants younger than 90 days with	**Results** Bacteremia = 9/1018 (0.88%) CRP (70g/L) Sensitivity (%) =	**Limitations** This study includes well appearing and unwell appearing children

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
bacteremia predictors in infants less than three months of age with fever without source, Pediatric Infectious Disease Journal, 29, 43-47, 2010 **Ref Id** 136096 **Country/ies where the study was carried out** Spain **Study type** Retrospective cohort study **Aim of the study** Objectives: (1) To assess the rate of bacteremia in febrile infants less than 3 months of age admitted to a pediatric emergency department at a tertiary hospital; (2) to describe the bacteria isolated; and (3) to analyze factors related to increased probability of having a positive blood culture **Study dates** September 2003 to August	Age <3 months **Inclusion Criteria** This study includes all infants younger than 90 days with a measured temperature 38.0°C at home or on arrival in the Pediatric Emergency Department. **Exclusion Criteria** Not reported	3. ANC **Reference test** Occult bacteremia - positive blood culture Bacterial meningitis - positive CSF culture, positive blood culture with pleocytosis UTI - Urine culture	a measured temperature 38.0°C at home or on arrival in the Pediatric Emergency Department are eligible for inclusion in the registry. Intervention: In the department, the algorithm for the management of infants less than 3 months of age with FWS recommends urine dipstick testing, CBC, CRP, blood culture, and urine culture for all children. The following were considered: lumbar puncture, including Gram stain, bacterial culture, viral culture, and enterovirus polymerase chain reaction, on an individual basis. If an infant was well-appearing, over 15 days old, and all ancillary tests appear to be normal, it was recommend that the patient be discharged without antibiotic treatment after several hours of observation in the Pediatric Emergency Department, generally up to 24 hours after fever developed (this means that if an infant is brought to the Pediatric Emergency Department 6 hours after fever was first registered, this infant remained in the Observation Unit for about 18 hours for clinical evaluation). Hospital admission is recommended for infants less than 15 days of age, those with abnormal laboratory tests and when the clinical situation worsens during the patient's stay in the Observation Unit. Although most guidelines recommend that all febrile infants under 28 to 30	69.6 (49.1 to 89.4) Specificity (%) = 93.8 (92.1 to 95.1) PPV (%) = 9 (2 to 15)* NPV (%) = 99.3 (98.5 to 99.6) LR+ = 10.7 (6.3 to 18.0)* LR- = 0.4 (0.1 to 0.9)* CRP (20g/L) Sensitivity (%) = 73.9 (53.5 to 87.5) Specificity (%) = 74.8 (72 to 77.5) PPV (%) = 3 (1 to 5)* NPV (%) = 100 (99 to 100)* LR+ = 3.1 (2.1 to 4.5)* LR- = 0.3 (0.1 to 1.0)* *All results were calculated by the NCC technical team	**Other information** 1125 infants were enrolled but blood culture was only performed in 1018 cases (91.5%) and in the 107 infants in whom blood culture was not performed were older. 1. Fever without source: axillary or rectal temperature at home, or rectal temperature in the Pediatric Emergency Department, of 38°C, without catarrhal or respiratory symptoms/signs (such as tachypnea) or a diarrheal process, in patients with normal physical examination, according to the diagnostic codes issued by the Spanish Society of Pediatric Emergencies (SEUP).22 Infants were included even if fever was assessed by parents at home without using a thermometer. The degree of sensitivity in terms of subjective fever assessments carried out by parents ranges between 74% and 84%, with a specificity of 76% to 96%.23,24 2. Well-appearing: defined by a normal paediatric assessment after being evaluated by a paediatric emergency physician during the first hour after attending the Pediatric Emergency Department. Appearance, respiratory and circulatory items had to be classified as normal for infants to be classified as well-appearing, and data had to be reflected on the patient's charts. 3. SBI = 198/1018 (19.4%); UTI = 172, Occult bacteremia = 9, UTI and bacteremia = 8, bacterial meningitis = 4, sepsis = 2, cellulitis = 2, acute otitis media = 1. Data were extracted from our registry of infants with FWS Younger than 3 months old. Infants younger than 90 days with a measured temperature 38.0°C at home or on

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
2008 **Source of funding** Not reported			days of age be hospitalized, 16- to 30-day-old infants at the Pediatric Emergency Department were observed in the Observation Unit, as explained above, and then either hospitalized or discharged depending on their clinical evolution.		arrival in the Pediatric Emergency Department are eligible for inclusion in the registry FWS: axillary or rectal temperature at home, or rectal temperature in the Pediatric Emergency Department, of 38°C, without catarrhal or respiratory symptoms/signs (such as tachypnea) or a diarrheal process, in patients with normal physical examination, according to the diagnostic codes issued by the Spanish Society of Pediatric Emergencies (SEUP).22 Infants were included even if fever was assessed by parents at home without using a thermometer. The degree of sensitivity in terms of subjective fever assessments carried out by parents ranges between 74% and 84%, with a specificity of 76% to 96%.23,24 • Well-appearing: defined by a normal pediatric assessment after being evaluated by a pediatric emergency physician during the first hour after attending the Pediatric Emergency Department. Appearance, respiratory and circulatory items had to be classified as normal for infants to be classified as well-appearing, and data had to be reflected on the patient's charts.
Full citation Manzano,S., Bailey,B., Gervaix,A., Cousineau,J., Delvin,E., Girodias,J.B., Markers for bacterial infection in children with fever without source, Archives of Disease in Childhood, 96, 440-446, 2011	**Sample size** n = 328 children (analysed); n = 457 enrolled and 129 dropped out **Characteristics** Median age (IQR) = 11 (6 to 17) months	**Tests** **Index test** 1. CRP 2. PCT 3. WBC 4. ANC 5. Clinical evaluation (using VAS)	**Methods** Recruitment: This study was part of a randomised controlled trial (RCT) assessing the impact of a rapid semi-quantitative PCT test on the management of children aged 1–36 months presenting to a paediatric emergency department with fever without source. Patient enrolment took place in the emergency	**Results** SBI = 54/328 (16%) UTIs - 48 Pneumonia - 4 Meningitis - 1 Occult bacteremia - 1 **PCT >0.20 ng/ml** Sensitivity = 85.2	**Limitations** 1. Not all markers were available in every patient as some were missing in 15% (56/384) of the children included in the RCT. **Other information** 1. It is estimated that among eligible children, over 90% had received at least three doses of the PCV7 vaccine against S

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 136132 **Country/ies where the study was carried out** Canada **Study type** Prospective cohort study **Aim of the study** To compare the diagnostic properties of procalcitonin (PCT), C reactive protein (CRP), total white blood cells count (WBC), absolute neutrophil count (ANC) and clinical evaluation to detect serious bacterial infection (SBI) in children with fever without source. **Study dates** November 2006 to November 2007 **Source of funding** Not reported	Mean temperature duration ± SD = 62±48 hours **Inclusion Criteria** To be included, the patient had to be a child between the ages of 1 and 36 months with a history of a rectal temperature over 38°C (100.4°F) with no identified source of infection after careful history taking and physical examination. **Exclusion Criteria** All patients with known acquired or congenital immunodeficiency, as well as children already treated with antibiotics, were excluded.	**Reference test** Bacteremia - positive blood culture UTI - urine culture Pneumonia - Chest radiography Bacterial meningitis - CSF culture Osteomyelitis - Positive bone scintigraphy Septic arthritis - Positive culture of synovial fluid	department of a tertiary care urban paediatric centre. Intervention: Attending paediatric emergency physicians approached the parents of children meeting the inclusion criteria to participate in the study. After consent was obtained, a blood test for complete blood count (CBC), semi quantitative PCT (for the RCT), CRP, blood culture and a bladder catheterisation or suprapubic aspiration for urine analysis and culture were performed. The attending physicians could perform any other investigations (such as lumbar puncture or chest radiography) as required and the decision to treat with antibiotics or to hospitalise was left to their discretion. A single venipuncture was performed. If this site was lost, or an insufficient amount of blood was drawn, no other attempt was made, as long as CBC and blood cultures were obtained. The attending physicians, all paediatric emergency physicians, were asked to evaluate the SBI probability with a visual analogue scale (VAS; 0–100%) after the history had been taken and a physical examination had been carried out, but before tests results were available. This comprised the subjective clinical evaluation. Laboratory technicians were blinded to the patients' final diagnosis.	(74.4 to 92.1) Specificity = 69.7 (67.6 to 71.1) PPV = 35.7 (31.2 to 38.6) NPV = 96.0 (93.1 to 97.9) LR+ = 2.8 (2.3 to 3.2) LR- = 0.2 (0.1 to 0.4) **CRP >17.7 mg/l** Sensitivity = 94.4 (85.5 to 98.1) Specificity = 68.6 (66.9 to 69.3) PPV = 37.2 (33.7 to 38.7) NPV = 98.4 (95.9 to 99.5) LR+ = 3.0 (2.6 to 3.2) LR- = 0.1 (0.03 to 0.2) <u>Children with normal urine analysis</u> SBI = 8/262 (3%) Pneumonia - 4 UTI - 2 Meningitis - 1 Bacteraemia - 1 **>0.20 ng/ml** Sensitivity = 87.5 (53.6 to 97.8) Specificity = 70.5 (69.4 to 70.8) PPV = 8.5 (5.2 to 9.5) NPV = 99.4 (97.9 to	pneumoniae and over 97% at least two doses. 2. Fever without source was defined as Rectal temperature >38°C (100.4°F) without any signs or symptoms identifying an infectious disease 3. SBI: Presence of bacteraemia, UTI, pneumonia, bacterial meningitis, osteomyelitis or septic arthritis 4. Because an SBI was found later in 8/262 (3%) children (four pneumonias, two UTIs, one meningitis and one occult bacteraemia) with normal urine analysis in the emergency department, and confirmed by the telephone follow-up carried out 1 week after the initial visit to the emergency department, the surrogate markers had better negative predictive values. 5. The investigators highlighted that urine culture and a lobar consolidation on chest radiography were not sufficient to classify or diagnose UTI and pneumonia or distinguish between bacterial and viral pneumonia. This could have influenced the real diagnostic properties of the markers used in our study. 6. The study took place in a paediatric emergency department of a large tertiary hospital. As results could be different in smaller community hospitals or other settings, it is not known if the results are generalisable. 7. **Authors conclusion**: "In our population of children 1 month to 3 years of age with fever without source, CRP, PCT, WBC and ANC had similar diagnostic properties to detect an SBI". (From the AUC data)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			CRP and PCT measurement were described in detail study was part of a randomised controlled trial (RCT) assessing the impact of a rapid semi-quantitative PCT test on the management of children aged 1–36 months presenting to a paediatric emergency department with fever without source.	99.9) LR+ = 3.0 (1.8 to 3.3) LR- = 0.2 (0.03 to 0.7) **CRP >17.7 mg/l** Sensitivity = 87.5 (53.6 to 97.8) Specificity = 69.7 (68.6 to 70.0) PPV = 8.3 (5.1 to 9.3) NPV = 99.4 (97.9 to 99.9) LR+ = 2.9 (1.7 to 3.3) LR- = 0.2 (0.03 to 0.7)	
Full citation Guen,C.G.-L., Delmas,C., Launay,E., Caillon,J., Loubersac,V., Picherot,G., Roze,C.J., Contribution of procalcitonin to occult bacteraemia detection in children, Scandinavian Journal of Infectious Diseases, 39, 157-159, 2007 **Ref Id** 136334 **Country/ies where the study was carried out** France	**Sample size** n = 215 analysed; 282 included and 67 excluded **Characteristics** Mean age = 15.2 ± 4.7 (3 to 36) months **Inclusion Criteria** Not reported **Exclusion Criteria** Immunocompromised children, children who had received antibiotics in the past 72 hours or appeared	**Tests** 1. WBC 2. CRP 3. PCT 4. WBC and ANC and/or CRP 5. PCT and or CRP 6. WBC and ANC and/or PCT 7. PCT and/or CRP and/or WBC and ANC. **Index test** **Reference test**	**Methods** The study was conducted at the paediatric medical and surgical emergency department of the Nantes Teaching Hospital, Nantes, France, which has about 25,000 visits per year. For the study, a urinary dipstick test was obtained for all patients aged 3 to 36 months who presented with unexplained fever of more than 39^{o}C documented in the emergency department or at home. The duration or length of fever was not considered in inclusion criteria. Patients whose dipstick test showed no leukocytes or nitrites underwent collection of a blood sample for a blood culture, a complete blood cell count, a serum procalcitonin	**Results** Prevalence of occult bacteremia - 7/215 (3.2%) Streptococcus pneumoniae - 4 Haemophilus influenzae b - 1 Neisseria meningitidis b - 2 <u>CRP ≥ 40mg/l</u> Sensitivity = 42.8±0.37 Specificity = 64.8±0.07 PPV = 3.8±0.22 NPV = 97.2±0.06 LR+ = 1.21 LR- =0.88	**Limitations** 1. It is not clear whether there was blinding in interpreting the results of any of the reference and or index tests **Other information** 1. **Authors conclusion**: "PCT alone failed to reliably discriminate between patients with and without bacteraemia. PCT may be a very early marker for bacteraemia; the median time from fever onset to blood sampling was only 4.6h in the patients with bacteraemia. Routine measurement of PCT in infants and toddlers with high-grade unexplained fever ensures the early diagnosis and treatment of patients who are at high risk for severe bacterial infection. At the same time, the unnecessary use of antibiotics is minimised, as negative tests consistently indicate

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study type Prospective cohort study **Aim of the study** To investigate the value of serum procalcitonin assay for diagnosing occult bacteremia in infants and toddlers with high grade fever of unknown origin. **Study dates** May 2004 to May 2005 **Source of funding** Not reported	to be in a toxic state were excluded		assay, and a serum CRP assay. Patients with suspected bacteremia were given empirical antibiotic therapy; when the result of the blood culture became available 48hr later, a decision was made about further antibiotic treatment. Patients without suspected bacteremia received antipyretic treatment and outpatient follow-up.	PCT ≥ 2mg/l Sensitivity = 57.1±0.37 Specificity = 86.4±0.05 PPV = 13.8±0.22 NPV = 98.1±0.06 LR+ = 4.19 LR- = 0.49 **Combined test results** PCT ≥ 2mg/l and or CRP ≥ 40mg/l Sensitivity = 71.4±0.33 Specificity = 61.4±0.07 PPV = 6.5±0.37 NPV = 98.2±0.06 LR+ = 1.85 LR- = 0.46	absence of bacteraemia."
Full citation Isaacman,D.J., Burke,B.L., Utility of the serum C-reactive protein for detection of occult bacterial infection in children, Archives of Pediatrics and Adolescent Medicine, 156, 905-909, 2002 **Ref Id** 149825 **Country/ies where the study was carried out**	**Sample size** n = 256 children (included); 266 children enrolled and 10 excluded **Characteristics** Median age (range) = 15.3 (3.1 to 35.2) months Median length of illness = 24 (0 to 288) hours **Inclusion Criteria** All febrile children who met entry criteria and required a complete blood cell count	**Tests** **Index test** 1. White blood cell count 2. Absolute neutrophil count 3. C-reactive protein **Reference test** 1. Bacteremia - blood culture 2. Pneumonia - Radiologic diagnosis 3. UTI - Urine culture	**Methods** Recruitment: Children visiting the emergency department of a free-standing, urban children's hospital, were eligible for participating this study. Intervention: Informed consent was obtained for each patient for the withdrawal of an additional 1-mL aliquot of blood sampled simultaneously for CRP measurement. C-reactive protein levels were measured using a heterogeneous immunoassay format; normal values using this assay are 0 to 0.9 mg/dL. Method: The determination as to whether a complete blood cell	**Results** OBI prevalence = 29/256 (11.3%) Pneumonia - 17 UTI - 9 Bacteremia - 3 CRP 4.4 Sensitivity (%) = 63 (43 to 82) Specificity (%) = 81 (76 to 87) PPV (%) = 30 (18 to 43) NPV (%) = 94 (91 to 98) LR+ = 3.3 (2.2 to 4.8)*	**Limitations** 1. It is not clear whether the test results were interpreted in a blinded manner **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
USA **Study type** Prospective cohort study **Aim of the study** To assess the utility of serum C-reactive protein as a screen for occult bacterial infection in children **Study dates** Not reported **Source of funding** This project was supported by grant 872090 from the Department of Paediatrics, Eastern Virginia Medical School, Norfolk	and blood culture as part of their evaluation were eligible for enrolment. **Exclusion Criteria** 1. Patients were excluded if they had taken any oral or parenteral antibiotics within 48 hours. 2. Immunodeficient patients were enrolled, but analysed separately.		count and blood culture were drawn, as well as other laboratory testing (including urinalysis and culture and chest radiograph), was made by the paediatric emergency medicine attending physician who was supervising the patient, and was based on standard guidelines adopted for the management of fever without apparent source in children of this age group. Housestaff and attending staff were informed that CRP levels were being analysed for study purposes only. Statistical analysis: The study was adequately powered	LR- = 0.5 (0.3 to 0.7)* *All results were calculated by the NCC technical team	
Full citation Pulliam,P.N., Attia,M.W., Cronan,K.M., C-reactive protein in febrile children 1 to 36 months of age with clinically undetectable serious bacterial infection, Pediatrics, 108, 1275-1279, 2001 **Ref Id**	**Sample size** n = 77 children **Characteristics** Mean age ± SD (range) = 9.7 ± 8.0 (1 to 35) months **Inclusion Criteria** Children who, after careful	**Tests** **Index test** 1. White blood cell count 2. Absolute neutrophil count 3. C-reactive protein **Reference test** Occult bacteremia - blood culture UTI - Urine culture	**Methods** Recruitment: A convenience sample of children who presented to the emergency department with temperature ≥39^{o}C was evaluated by residents and paediatric emergency medicine attending. Intervention: Total Wbc, band count, ANC, and quantitative CRP concentration were obtained. All patients received a blood culture and either a screening urinalysis or urine culture. Urine was	**Results** SBI prevalence = 14/77 (18%) UTI - 6 Pneumonia - 4 (1 case with pneumonia and bacteremia) Occult bacteremia - 4 CRP 7 mg/dL Sensitivity (%) = 79	**Limitations** No limitations **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
149827 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** To prospectively study the diagnostic properties of quantitative CRP in comparison with other clinical and laboratory predictors of occult SBI in young children with fever without apparent source of infection. **Study dates** January 1, 2000 to October 31 2000 **Source of funding** The study was funded by resarch grant W20-8619 from the Nemours Research Programs, Wilmington, Delaware.	history and physical examination, had clinically undetectable source for the fever. **Exclusion Criteria** Children with acute otitis media, acute pharyngitis, clinical pneumonia, acute respiratory tract infection, acute grastroenteritis, and those with a history of antibiotic use during the past 7 days, a known underlying immunologic disease, or who received vaccination during the previous 2 days were excluded	Pneumonia - Chest x-ray	obtained by urethral catheterisation using standard sterile technique. Chest radiographs as well as other laboratory and radiographic tests were obtained at the discretion of the ED physician. Method: Laboratory personnel and radiology staff were blinded to clinical information. Statistical analysis: Sample size was estimated using a pre-test probability for SBI of 10% and a hypothesized sensitivity of 100% for the CRP level. Given these figures; 80 patients needed to be enrolled including a narrow 95% confidence interval.	(49 to 94.2) Specificity (%) = 91 (79.8 to 96) PPV (%) = 65 (38.3 to 85.8) NPV (%) = 95 (86.1 to 99) LR+ = 8.3 (3.8 to 27.3) LR - = 0.2 (0.1 to 0.6)* *All results were calculated by the NCC technical team	
Full citation Hsiao AL, Chen L, Baker MD., Incidence and predictors of serious	**Sample size** n=429	**Tests** **Index test**	**Methods** <u>Recruitment</u> - Infants 57-180 days of age with rectal temperatures >37.9C who	**Results** <u>SBI</u>= 44/429 (10.3%)	**Limitations** - CRP data missing for 42 subjects (9.8%)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
bacterial infections among 57- to 180-day-old infants., Pediatrics, 117, 1695-701, 2006 **Ref Id** 156469 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** To establish the epidemiology of febrile illnesses and to evaluate the usefulness of screening tests in this population. **Study dates** February 2003-February 2004 **Source of funding** Not reported	**Characteristics** Age: 57-180 days (2-6months) Mean duration of fever in hours +/- SD: 26.5 +/- 41.5 (Infants with SBI) 18.6 +/- 21.7 (Infants without SBI) **Inclusion Criteria** - Age 57-180 days (2-6 months) - Rectal temperature > 37.9C **Exclusion Criteria** - Children whose families chose not to participate	C-reactive protein (CRP) **Reference test** - Blood cultures - Urinalysis and urine culture - CSF cultures - Chest radiograph, lumbar puncture and stool studies were performed at the discretion of the attending physician	consecutively presented to the emergency department of Yale-New Haven Children's Hospital were prospectively enrolled after informed consent. - All children underwent a complete evaluation including history and physical examination and scoring of clinical appearance using the Yale Observation Scale (YOS) by an attending-level faculty experienced in its use. Laboratory evaluation - A standard laboratory evaluation including complete blood count with differential, latex particles in antibody assay for CRP, blood cultures, and urine for urinalysis and urine culture was also carried out. Additional studies such as chest radiograph, lumbar puncture, and stool studies, were performed at the discretion of the attending physician. - Bacterial culture results were monitored until their completion, typically 2 days for urine cultures and 5 days for blood and cerebrospinal fluid cultures. Urine cultures were considered positive if there were >10000 colonies of a single organism per mL. Positive culture results were reported to the paediatric emergency department physician staff and primary care paediatrician. Other information - Clinicians were asked to note	Bacteremia=4 Bacteruria=41 CRP ≥0.98mg/dL Sensitivity = 51.2 (35.9 to 66.5)* Specificity= 19.7 (15.5 to 23.8)* PPV= 7.0 (4.1 to 9.9)** NPV= 77.2 (68.5 to 86.0)** LR+= 0.64 (0.47 to 0.86)** LR-= 2.48 (1.70 to 3.63)** *Confidence intervals calculated by NCC technical team **All results calculated by NCC technical team	**Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			the presence or absence of an obvious source of fever after physical evaluation of the patient and before return of laboratory or other studies. - Age, gender, laboratory results, historical details and physical examination findings were recorded. - Discharged patients with positive blood cultures were contacted and instructed to return to the PED for re-evaluation and subsequent management. Computerized hospital records were used to obtain duration of inpatient stays and ultimate diagnoses and were monitored for return visits to the PED within 14 days, regardless of the chief complaint. - The data were analysed using SPSS 12.0 for Windows. Independent t test comparison of means for potential SBI indicators was used.		
Full citation Berger RM, Berger MY, van Steensel-Moll HA, Dzoljic-Danilovic G, Derksen-Lubsen G., A predictivemodel to estimate the risk of serious bacterial infections in febrile infants., European Journal of Pediatrics, 155, 468-73, 1996	**Sample size** n=138 **Characteristics** Age: 2 weeks-1 year **Inclusion Criteria** - Infants aged 2 weeks-1 year	**Tests** **Index test** -CRP **Reference test** -Urine culture -Blood samples, nose and throat swabs and stool specimens were cultured	**Methods** - Data on history, observation and physical examination were obtained using a standard form. - Clinical impression was standardised using a modification of variables proposed by McCarthy et al - Laboratory data included WBC and differential counts, ESR, C-	**Results** SBI prevalence= 33/138 (24%) CRP>20mg/l Sensitivity= 83.3 (70.0-96.7)* Specificity= 67.0 (57.7-76.4)* PPV= 43.9 (31.0-56.7)**	**Limitations** -CRP data missing for 11 subjects **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 156470 **Country/ies where the study was carried out** Netherlands **Study type** Prospective cohort study **Aim of the study** To determine independent predictors of SBI in febrile infants using multivariate logistic regression analysis. **Study dates** Not reported **Source of funding** Not reported	- Rectal temperature >/=38C **Exclusion Criteria** - Infants who were born preterm (gestational age <37 weeks) - Infants who had perinatal complications - Infants who received antibiotics or had been vaccinated in the 48 hours preceding the visit - Infants with a known previous or underlying disease	-Lumbar puncture and chest radiography were left to the discretion of the house officer -Tympanocenthesis was performed if suggested by the ENT consultant -Joint fluid and skin were cultured when arthritis or skin lesion respectively were suspected	reactive protein and urinalysis. Urine was cultured when the urinalysis was positive. Blood samples, nose and throat swabs and stool specimens were cultured. Lumbar puncture and chest radiography were left to the discretion of the house officer, and tympanocenthesis was performed if suggested by the ENT consultant. Joint fluid and skin were cultured when arthritis or skin lesion respectively were suspected. - All infants were re-evaluated 14 days after presentation. - The outcome variable was SBI, defined as bacterial growth in cultures from blood, CSF or urine or as growth of Salmonella, Shigella or Campylobacter species in stool. - Urinary tract infection was defined by a urine culture with >/=10^5 colonies/ml of a single organism. - Presumptive clinical diagnosis of otitis media, cellulitis, arthritis and osteomyelitis was regarded as SBI only in combination with bacterial growth in specimen culture from middle ear aspirate, soft tissue, joint and bone respectively. - Infants with a chest roentgenogram yielding pulmonary infiltrate, confirmed by	NPV= 92.9 (86.8-98.9)** LR+= 2.53 (1.82-3.50)** LR-= 0.25 (0.11-0.56)** *Confidence intervals calculated by NCC technical team **All results calculated by NCC technical team	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			an attending radiologist were considered as having serious illness and included in the SBI group. - Staphylococcus epidermis and other skin commensals were considered to be contaminants in this population of previous healthy infants. Those who defined the outcome were blinded for the predictive findings. - The results were compiled by a pre-designated format, and subjected to univariate and multivariate analyses. The variables introduced in the logistic regression model were those with perceived clinical relevance, those identified by the univariate analysis or those reported as of diagnostic value by others.		
Full citation Woelker,J.U., Sinha,M., Christopher,N.C., Powell,K.R., Serum procalcitonin concentration in the evaluation of febrile infants 2 to 60 days of age, Pediatric Emergency Care, 28, 410-415, 2012 **Ref Id** 191094 **Country/ies where the study was carried out**	**Sample size** 819 potential patients; 159 recruited; 155 eligible for analysis **Characteristics** Age, mean (SD), years = 30.72 (16.59) Sex, male, n (%) = 91 (58.7) Length of stay, mean (SD)	**Tests** PCT **Index test** PCT = immunoluminometric assay (BRAHMS LUMI test). All measured within 13 months of collection. Rochester Criteria list SBI **Reference test** SBI defined as: positive blood	**Methods** <u>Ethics</u> Ethical approval and informed consent obtained <u>Setting</u> Single ED department in USA	**Results** 13 with SBI - 11 had UTI, 2 had bacteremia 132 without SBI PCT ng/mL; Sensitivity (95%CI); Specificity (95%CI) 0.20; 1 (0.72 to 1.00); 0.41 (0.33 to	**Limitations** Majority of eligible patients were not included in study. Main SBI was UTI **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
USA **Study type** Prospective cohort study **Aim of the study** Investigate sensitivity and specificity of PCT to find the optimum cutoff using ROC curve. **Study dates** Patients recruited between May 2004 to March 2007 **Source of funding** Grant from Akron Children's Hospital	2.3 (4.94) **Inclusion Criteria** Aged 2 to 60 days Rectal temperature >= 38C Appear well **Exclusion Criteria** Not stated	or CSF culture, bacterial pathogen in stool, or positive urine culture with greater than 50,000 colony forming units/mL of a single pathogen or 10,000 to 49,000 with a positive urinalysis.	<u>Statistical methods</u> ROC curve Sensitivity and specificity using Wilson score with continuity correction Logistic regression used for RC score <u>Outcomes</u> Diagnostic value of PCT compared to final diagnosis Rochester criteria	0.49) 0.26; 0.92 (0.62 to 1.00); 0.64 (0.55 to 0.72) 0.30; 0.85 (0.54 to 0.97); 0.67 (058 to 0.74) Results for other tests not reported	

Chapter 8

Response to antipyretic medication

Review question

What is the predictive value of the clinical response to paracetamol or NSAIDs?

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
Full citation Torrey 1984 Ref ID Country/ies where the study was carried out USA Study type Prospective cohort Aim of the study Hypothesis that antipyretic therapy would be less effective on lowering body temperature in patients with bacteremia Study dates July 1980 to March 1981 Source of funding Not stated	**Sample size** 255 (16 with occult bacteremia and 239 without) Characteristics Bacteremia vs. Non-bacteremia <u>Age (months):</u> 10.8; 11.5 <u>Gender:</u> N/A Diagnosis: See recruitment Inclusion criteria Children age 3 to 24 months Temperature of >38.9°C Exclusion criteria Children with serious focal infections requiring admission to hospital	**Interventions** <u>Diagnostic evaluation</u> Two blood samples taken for culture using 1) Brucella broth with 7% sorbitol 2) Columbia broth. Samples incubated then examined for growth. Those showing signs evaluated using Gram's stain and sub-cultured aerobically and anaerobically. <u>Intervention</u> 10 mg/kg acetaminophen or aspirin at time of baseline temperature measurement <u>Temperature measurement</u> At baseline then 60 to 120 minutes after baseline	**Details** <u>Recruitment:</u> Setting was a hospital emergency department. 516 evaluated 255 with complete data 16 had positive blood cultures 12 with streptococcus pneumonia 2 with Haemophilus influenza 2 with Salmonella Of 261 with missing data, 205 second temperature was not measured. <u>Methods:</u> Temperature measured rectally using electronic digital thermometer. No blinding reported No sample size calculation reported <u>Statistical analysis:</u> Chi-squared test and Student's t-test.	**Results** 255 included, 16 with bacteremia and 239 without. <u>Baseline temperature</u> 40.1 vs. 39.9 (p=0.04) <u>2nd Temperature</u> 38.8 vs. 38.8 (p=0.46) <u>Change in temperature</u> 1.32 vs. 1.05 (p = 0.14) Change in temperature > 1°C (p = 0.90)	**Limitations** No blinding of assessment High drop-out rate Follow-up measurement at different times Different treatment used Other information Authors – response to antipyretics does not distinguish illness Confidence intervals reported. Data not reported for reanalysis.

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
Full citation Baker 1989 Ref ID **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** Hypothesis that persistent clinical appearance of illness despite fever reduction is a reliable sign of occult bacteremia in the febrile infant. **Study dates** September 1986 to January 1988 **Source of funding**	**Sample size** 154 children (135 non-bacterial, 15 bacteremia, 4 meningitis) **Characteristics** **Age:** 12 months **Gender:** Not reported **Diagnosis:** See recruitment Inclusion criteria Children aged 3 to 24 months Temperature >39.4°C No history of antibiotic use within preceding 48 hours Exclusion criteria Children with signs of meningitis or septic	**Interventions** Diagnostic evaluation Vital signs Yale Observation Score Mandatory laboratory evaluations – CBC count, blood culture, urinalysis. Optional tests – lumbar puncture and chest roentgenography. (Only results from temperature being reported here) **<u>Intervention</u>** Oral or rectal 15 mg/kg acetaminophen **<u>Temperature measurement</u>** Baseline then one to two hours after treatment. Method of measurement not outlines	Details Recruitment: Setting was a paediatric emergency department Convenience sample 154 of which 19 with bacteremia, of which 4 had meningitis 13 had Streptococcus pneuminaie 6 had Haemophilus influenzae **Methods**: Ethical approval gained Blinding of assessment not mentioned Sample size calculation not mentioned **Statistical analysis:** Student’s t-test to compare continuous outcomes or one-way ANOVA to compare means	**Results** Outcome, Non-bacterial (n = 135), bacterial (n = 15), meningitis (n = 4) Temperature Baseline 40.0 (SD +/- 0.4), 40.1 (SD +/- 0.5), 40.0 (SD +/- 0.3) 2nd Temperature 38.4 (SD +/- 0.6), 38.5 (SD +/- 0.6), 38.7 (SD +/- 0.7) Change in temperature -1.6 (SD +/- 0.6), -1.7 (SD +/- 0.8), -1.3 (SD +/- 0.8) No difference YOS Baseline 9.3 (+/- 2.9), 11.3 (+/- 3.5), 17.5 (+/-4.7)	Limitations -Children with meningitis included in analysis even though excluded from study. - Timing of temperature measurement varied. - blinding not mentioned Other information

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
Not stated	shock		Outcomes: Difference in 2nd temperature and change in temperature.	2nd Temperature 7.7 (+/- 2.2), 7.5 (+/- 1.4), 19.5 (+/-5.9) Change -1.6 (+/- 2.5), -3.8 (+/- 3.2), +2.0 (+/-1.6) Meningitis different from other groups. p <0.02	
Full citation Yamamoto, 1987 Ref ID **Country/ies where the study was carried out** USA **Study type** Prospective cohort **Aim of the study** Hypothesis that children whose temperatures do not	**Sample size** 332 Characteristics Of 233 included in analysis Number of subjects = Total = 233, + blood culture = 17, - blood culture = 216 **Age**: 12.5 (SD +/- 4.99), 13.5 (SD +/- 4.68), 12.5 (SD +/-5.02). p=0.09 Gender (male, n): 129 of 233, 9 of 17, 120	**Interventions** Diagnostic evaluation All children have WBC and one blood culture using Bactec system. Cultures were negative if no growth after 7 days. Children followed-up at 48 to 96 hours by telephone or chart review. **Intervention** 10 to 15 mg/kg acetaminophen. If given antipyretic between 2 or 4 hours before presentation then given a different one. Children treated within 2 hours of presentation were not given a further dose Children who vomited were given a rectal dose Temperature measurement	**Details** Recruitment: Setting was children seen 1) at acute care clinic or 2) an emergency department 332 eligible. 37 were missed and 29 refused participation. 33 patients excluded from analysis due to protocol violations or missing data. **Methods**: Ethical approval and consent gained Blinding of assessment not mentioned Sample size calculation not mentioned	**Results** Number of subjects Total = 233, + blood culture = 17, - blood culture = 216 No difference between settings Baseline temperature 40.36 (SD +/- 0.297), 40.48 (SD +/- 0.356), 40.35 (SD +/- 0.290) p = 0.09 Change in temperature 1.636 (+SD /- 0.704), 1.606 (SD +/- 0.722), 1.639 (SD +/- 0.705)	**Limitations** Intervention varied between subjects Timing of 2nd reported temperature measurement not defined. Blinding of assessment not mentioned Sample size calculation not mentioned Other information

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
respond to antipyretic therapy have an increased prevalence of bacteremia. **Study dates** November 1983 to September 1984 **Source of funding** Grant from Christ Hospital Medical Education Fund	of 216 **Diagnosis:** Groups divide based on diagnosis **Inclusion criteria** Aged 3 to 24 months Temperature ≥ 40°C Not taking antibiotics **Exclusion criteria** Not stated	Temperature measured rectally hourly during visit Children followed-up 48 to 96 hours via telephone or medical records.	**Statistical analysis:** Categorical used chi squared test; continuous used Student t-test. **Outcomes** Change in temperature Change of 1°C in temperature	p= 0.85 Non-response of 1°C to treatment 2/17, 36/216. P = 0.598	
Full citation Mazur, 1989 Ref ID **Country/ies where the study was carried out** USA **Study type** Retrospective case-control study **Aim of the study** Hypothesis that children whose fever does not	**Sample size** 34 case with + blood culture and 68 controls with – blood culture Characteristics Age (months): 15.6, 15.5 Gender: Male 22, 40 Female 12, 28 Diagnosis: Used for analysis	**Interventions** Diagnostic evaluation Blood culture **Intervention** Centre's fever protocol "Children with temperature ≥ 38.9C shall be given acetaminophen at a dose of 10 mg/kg if they have not been medicated within the past 4 hours. The temperature is rechecked and recorded within 2 hours and when the child leaves the emergency room." Temperature measured using digital thermometer	**Details** **Recruitment**: Setting was a children's hospital serving as primary and tertiary centre. 33,813 visits to center 3,892 febrile patients aged between 2 months and 6 years. 2,101 had blood culture 1,028 were eligible **Methods**:	**Results** Cases vs. controls Comparison of diagnostic groups Groups were balanced in terms of diagnosis Mean time to 2nd measure 80.1 minutes (SD 34.8 or 22.9, respectively) Mean dose of acetaminophen was 10.4	**Limitations** Retrospective design No blinding Other information

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
respond to acetaminophen have at least a seven-fold increase in the risk of occult bacterema. **Study dates** May 1986 to October 1987 **Source of funding** Not stated	**Inclusion criteria** Temperature ≥ 38.9C Aged between 2 and 6 years Blood culture obtained Fever protocol followed. **Exclusion criteria** Sickle cell anaemia, cystic fibrosis, cancer, immunodeficiency syndrome, meningitis, cellulitis or osteomyelitis. Children sponged to reduce temperature, vomited after receiving acetaminophen, or taking antibiotics or corticosteroids.		**Statistical analysis:** Sample size calculation required 35 cases and 70 controls. Positive cases identified from case review. Negative controls matched for age (+/- 2 months), temperature at presentation (+/- 0.6 C) and month of presentation (+/- 1 month). Univariate and multivariate regression analysis (dose of acetaminophen and time to 2nd measurement). **Outcome** Comparison of mean change in temperature Comparison in response to treatment of ≤0.8°C	(SD +/- 1.8) mg/kg vs. 10.6 (SD +/- 1.5) mg/kg Baseline temperature 39.8°C (SD +/- 0.5) for both groups Mean temperature decrease 1.0 (SD +/- 0.6) vs. 1.5 (SD +/- 0.5), p = 0.0005) Response to acetaminophen Univariate OR = 9.2 (95% CI 2.7 to 32.0) Multivariate OR = 9.4 (95% CI 2.6 to 34.2)	
Full citation Weisse, 1987 Ref ID **Country/ies where the study was carried out** USA	**Sample size** 100 **Characteristics** Age: Range 9 days to 17 years. Median age was 2 years.	**Interventions** Diagnostic evaluation Diagnostic tests ordered at discretion of physician. Tests included: bacterial from pharynx or tonsils; and viral cultures from nasal or stools; blood cultures using BACTEC system.	**Details** Recruitment: Setting at a paediatric clinic 100 enrolled, 81 with blood cultures, WBC in 79 and viral studies in 65. **Methods:**	**Results** 16 with culture + viral illnesses (including 2 with asceptic meningitis) 49 with symptoms of viral illness 17 with culture + bacterial illness 18 with symptoms of	**Limitations** Included children outside specified age range. Not all children had reference tests. Non-systematic reporting of results

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
Study type **Aim of the study** Hypothesised that there is no difference in antipyretic response between viral and bacterial infections **Study dates** September 1985 to October 1986 **Source of funding** Not stated	**Gender:** Diagnosis: **Inclusion criteria** Oral or rectal temperature of ≥ 39.8C **Exclusion criteria** Received antibiotics or antipyretics within 3 years.	Intervention 15 mg/kg of acetaminophen with maximum of 650 mg	**Statistical analysis:** Student's t-test to compare viral and bacterial groups. Linear regression used to correlate WBC and erythrocyte sedimentation rate with temperature change. Proportion of afebrile in each group assessed using chi-squared. Analysis split on those with culture + results only then all patients.	bacterial illness Mean change in culture + viral was 1.16°F and + bacterial was -1.48°F, p = 0.37. Not difference when clinical symptoms cases included. Proportion of patients becoming afebrile (<100.4°F). 4 of 35 vs. 10 of 65 (NS)	Other information
Full citation Baker, 1987 Ref ID **Country/ies where the study was carried out** **Study type** Prospective cohort **Aim of the study** Investigate whether or not	**Sample size** 1559 **Characteristics** Age: 8 weeks to 83 months <12 months – 34% 12 to 23 months – 22% 24 to 35 months – 17% 36 to 47 months – 11% 60 to 71 months – 5%	**Interventions** Diagnostic evaluation Diagnostic evaluation was at discretion of physician and included various tests. Diagnosis based on chart review and contact with parents. **Intervention** 15 mg/kg oral acetaminophen. Children who vomited within 30 minutes were remedicated.	**Details** **Recruitment:** Setting 1) paediatric emergency room and 2) walk-in clinic 3,911 evaluated 2,055 were eligible. 76 missed and 420 discharged within 1 hour. 1,559 had repeat temperature at 1 hour 471 had repeat temperature at 2 hours	**Results** Diagnosis – baseline temperature, 1 hour change (°C), 2 hour change (°C) Group A B-hemolytic streptococcus pharyngitis – 39.3 (SD +/- 0.5), 1.3 (SD +/- 0.5)*, 1.4 (SD +/- 0.4) Culture-positive bacterial disease – 39.7 (SD +/- 0.8), 1.3 (SD +/- 0.8)*, 1.8 (SD +/- 0.5)*	**Limitations** Subjects were not required to stay for completion of study. Diagnosis was not based on single 'gold' standard reference test. Reference tests not described in detail. Missing values not reported.

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
temperature response to acetaminophen administration varies by disease process. **Study dates** October 1984 to September 1985 **Source of funding** Not stated	72 to 83 months – 3% **Gender:** Male – 850 Female - 709 **Diagnosis:** Viral syndrome – 30% Otis media – 27% Viral diseases – 15% Pneumonia – 11% Non-cultured gastroenteritis – 10% Culture-positive bacterial disease – 4% Group A B-hemolytic streptococcus pharyngitis – 3% **Inclusion criteria** Rectal temperature > 38.4°C Not received antipyretics within 4 hours of presentation Exclusion criteria Not stated		**Methods:** Ethical approval obtained Informed consent obtained Physicians blinded to temperature measurement **Statistical analysis:** Chi-squared and analysis of variance. P<0.5	Non-cultured gastroenteritis – 39.5 (SD +/- 0.6), 1.1 (SD +/- 0.6), 1.4 (SD +/- 0.7) Pneumonia – 39.6 (SD +/- 0.7), 1.2 (SD +/- 0.6)*, 1.8 (SD +/- 0.6)* Viral diseases – 39.6 (SD +/- 0.6), 1.0 (SD +/- 0.6), 1.4 (SD +/- 0.7) Otis media – 39.6 (SD +/- 0.4), 1.0 (SD +/- 0.6), 1.6 (SD +/- 0.7) Miscellaneous – 39.5 (SD +/- 0.4), 1.0 (SD +/- 0.6), 1.6 (SD +/- 0.7) TOTAL – 39.5 (SD +/- 0.6), 1.0 (SD +/- 0.6), 1.6 (SD +/- 0.7) *p < 0.01	Other information Authors “Differences are not clinically useful”.

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
Full citation Mazur, 1994 Ref ID **Country/ies where the study was carried out** USA **Study type** Retrospective cohort **Aim of the study** Comparison of temperature and WBC as markers of occult bacteremia. **Study dates** May 1986 to October 1987 **Source of funding** Not stated	**Sample size** Characteristics Occult bacteremia (n = 34) vs. without occult bacteremia (n = 450) Age (mean, months): 15.6 vs. 19.9. Gender: Male 22 vs. 224 Female 12 vs. 206 Diagnosis: Used in analysis Inclusion criteria Temperature ≥ 38.9°C Aged between 2 and 6 years Blood culture obtained Fever protocol followed. Not antipyretics within previous 4 hours Exclusion criteria	**Interventions** Diagnostic evaluation Gold standard was blood culture results Temperature measured either orally (> 3 years) or rectally (<3 years) using a digital thermometer accurate to +/- 0.1°C. WBC only measured once, so not included in assessment of antipyretics. **Intervention** Acetaminophen 10mg/kg	**Details** **Recruitment**: Setting was a children's hospital serving as primary and tertiary centre. **Methods:** Ethical approval obtained No sample size calculation Blinding of analysis not mentioned **Statistical analysis:** Continuous variables using t-test, categorical using chi-squared. Diagnostic accuracy using sensitivity specificity, PPV and NPV Multivariate regression analysis to adjust for temperature response, dose and time to second measurement. ROC curves for temperature response using cut-offs of 0.5°C 1.0°C, 1.5°C, 2.0°C and 2.5°C	**Results** Baseline temperature 39.8°C (SD +/- 0.5) with OB and 39.7°C (SD +/- 0.5) without OB Average time to second measurement 80 minutes (SD +/- 35) vs. 86 minutes (SD +/- 34) Average dose of acetaminophen was 11.1 (SD +/- 1.8) mg/kg vs. 11.3 (SD +/- 2.1) mg/kg) Average temperature changes -1.0°C (SD +/- 0.6) vs. -1.2°C (SD +/- 0.6) Risk analysis of 0.8°C response to acetaminophen Univariate OR = 2.6 (95% CI 1.3 to 5.2) Multivariate OR = 3.4 (95% CI 1.6 to 7.3)	**Limitations** Retrospective design Children outside specified age-group included Other information Uses same case population as the 1988 study Author conclusion - response to antipyretics is not predictive of bacterial illness.

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
	Sickle cell anaemia, cystic fibrosis, cancer, immunodeficiency syndrome, meningitis, cellulitis or osteomyelitis. Children sponged to reduce temperature, vomited after receiving acetaminophen, or taking antibiotics or corticosteroids.		Outcome Mean change in temperature Response to antipyretics of -0.8°C Sensitivity, specificity, PPV, NPV	Diagnostic outcome based on 0.8 °C response to acetaminophen Sensitivity = 47% Specificity = 74%, PPV = 12% and NPV = 95% Diagnostic outcome based on WBC of 15,000/ul and 0.8°C response after to acetaminophen Sensitivity = 33% specificity = 63%, PPV = 25% and NPV = 72%	
Full citation Bonadio, 1993 Ref ID Country/ies where the study was carried out	**Sample size** 140 (Bacterial meningitis = 22, Isolated bacteremia = 59, Non-bacterial febrile illness = 59) Characteristics	**Interventions** Diagnostic evaluation Diagnosis based on clinical evaluation and blood cultures. Intervention 10 to 15 mg/kg acetaminophen	**Details** Recruitment: Setting was a paediatric emergency department Methods:	**Results** Bacterial meningitis (n = 22) mean -1.06°C, median -0.80°C, Isolated bacteremia (n = 59) -1.40°C -1.30°C, Nonbacterial febrile illness (n = 59) -1.44°C, -	**Limitations** Groups identified from different time periods in order to obtain sufficient cases. Different treatment dosage calculation. Different timings of

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
USA Study type Retrospective cohort Aim of the study Compare change in body temperature after acetaminophen in febrile children based on clinical diagnosis. Study dates 1986 to 1992 Source of funding Not stated	Bacterial meningitis, Isolated bacteremia Nonbacterial febrile illness Age (mean, months): 8.8, 9.9, 10.4 Gender: Not stated Diagnosis: Used for analysis Inclusion criteria 2 to 24 months Fever ≥ 39.0°C rectal temperature Received 10 to 15 mg/kg acetaminophen Had repeat temperature measurement 60 to 90 minutes after treatment Exclusion criteria Received antipyretics within 4 hours of evaluation Using antibiotics or		Ethical and consent not mentioned Sample size not mentioned Blinding of assessment not mentioned Statistical analysis: Sample size calculation not mentioned ANOVA using Krustal-Wallis test to compare median values. Linear regression used to adjust for age and temperature change. Outcomes: Change in temperature	1.40°C No statistical difference between groups	temperature measurement. Reference tests not described in detail and could vary. Other information

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
	corticosteroids prior to repeat measure.				

Chapter 9 Antipyretic interventions

9.1 Effects of body temperature reduction

Review question

Whether reducing fever with paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) affects the course of the disease?

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
Full citation Dubos 2008 **Ref ID** **Country/ies where the study was carried out** France **Study type** Prospective cohort **Aim of the study** To determine the incidence rate of hospitalization for patients with secondary bacterial skin complications related to varicella, and potential risk-factors **Study dates** 2003 **Source of funding** Not stated	**Sample size** 159 43 with varicella and skin infection 116 with varicella alone (50 with other varicella related complications) **Characteristics** **With skin infection vs. no skin infection** Age (months): 28; 24 (NS) Gender (% male): 54; 72 (p=0.04) Fever (=> 38.5C, %) 39; 64 (p = 0.006) **Diagnosis:** See recruitment **Inclusion criteria** Children aged less than 16 years Presenting with varicella **Exclusion criteria** None	**Risk factors assessed** Age, gender, underlying condition, sibling case, previous advice, use of aspirin, steroids, antibiotics, antivirals, antiseptics, colorants, powders or creams, paracetamol, ibuprofen, fever, mucous lesions and vesicles.	**Details** Setting 11 district hospitals Recruitment: Methods: Observational Data collection Clinician completed questionnaire Outcomes Varicella defined as generalised pruritic vesicular rash with mild fever. Secondary bacterial skins infections defined as: cellulitis, necrotising fasciitis, staphylococcal or streptococcal toxin mediated disease, skin abscess, ecthyma and varicella gangrenosa. Statistical analysis: Chi-squared test and Student's t-test. Multivariate analysis only included variables that were significant in univariate analysis	**Results** Univariate analysis Paracetamol 4.3 (0.9 to 28) Ibuprofen 4.1 (1.4 to 12 Age < 24 months 0.2 (0.1 to 0.7) Fever =>38.5C for => 3 days 6.2 (1.8 to 24) Mucous lesions 2.8 (0.9 to 8.4) Vesicles >100 3.6 (1.3 to 10) Non-significant factors Gender, underlying condition, sibling case, previous advice, use of aspirin, steroids, antibiotics, antivirals, antiseptics, colorants, powders or creams Multivariate analysis adjusted OR Age < 24 months 0.2 (0.05 to 0.5) Fever =>38.5C for => 3 days 8.1 (2.3 to 28.4) NSAIDs 4.8 (1.6 to 14.4)	**Limitations** Observational study design Not linked with disease severity Only adjusted for significant co-variates rather than plausible confounders. **Other information**
Full citation Mikaeloff, 2007	**Sample size** 156,034 with primary varicella 129,684 with zoster	**Interventions** Recorded use of NSAID or Paracetamol	**Details** **Recruitment:** Setting General practice	**Results**	**Limitations** Study based on GP database, so OTC or hospital

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
Ref ID **Country/ies where the study was carried out** France & Canada. Data from the UK **Study type** Retrospective case-control **Aim of the study** Determine whether NSAIDs could increase the risk of severe skin or soft tissue complications in patients with varicella or zoster **Study dates** Patient records from January 1994 to December 2005 **Source of funding**	disease **(**only varicella data reported, as this relates to children) **Characteristics** Age: 10.7 (14.5); 11.4 (15.0) Gender (% female): 47.67; 49.13 Gastrointestinal disorder (%): 2.07; 1.08 **Diagnosis:** **Inclusion criteria** Varicella or zoster diagnosis recorded **Exclusion criteria** Chronic hepatic insufficiency or chronic renal insuffiency		**Methods:** 2 month follow-up after initial presentation with varicella or zoster. Prescriptions of NSAIDs or paracetamol recorded on database **Statistical analysis:** • Logistic regression • NSAIDs users compared with non-users • Adjusted for sex, prescription history in previous year, and co-morbidities **Outcomes:** Skin or soft tissue complications		prescriptions not recorded. **Other information**
Full citation Francois, 2010 **Ref ID** **Country/ies where the study was carried out** France **Study type** Retrospective cohort	**Sample size** 767 included in analysis • 677 with uncomplicated pneumonia • 90 with complicated pneumonia **Characteristics** **Age:** 4.1 (2.0 to 6.6); 3.0 (1.3 to 5.6) **Gender (male, n):**	**Interventions**	**Details** **Recruitment:** Medical records from 2 hospitals **1184 records with pneumonia** • 69 excluded due to missing data • 348 excluded due to clinical characteristics (LRTI, no clinical inclusion criteria, hospital acquired pneumonia, age < 28 days **767 analysed** • 677 with uncomplicated pneumonia • 90 with complicated pneumonia	**Results** **Multivariate** **Amino-penicillin** 1.57 (0.91 to 2.72) **Cephalosporin** (1.24 (0.67 to 2.30) **Macrolide 1**.26 (0.58 to 2.73) **Other antibiotics** 2.19 (0.53 to 9.14) **Ibuprofen** 2.57 (1.51 to 4.35) **Aspirin** 1.72 (0.69 to 4.99) **Glucocorticoids** 1.41 (0.58	**Limitations** **D** **Other information**

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
Aim of the study Identify baseline characteristics associated with suppurative complications **Study dates** January 1995 to December 2003 **Source of funding** Not reported	60; 55.1 **Fever duration (days)** 3 (2 to 5); 6 (4 to 10) **Anti-inflammatory use** 36.7; 14.3 (p < 0.001) **Diagnosis:** **Inclusion criteria** ICD-10 code for pneumonia (complicated or uncomplicated) Validated based on radiographic findings and presence of fever, cough or thoracic pain. **Exclusion criteria** Hospital acquired pneumonia Lower respiratory tract infection secondary to an inherent illness (asthma, etc.)		**Methods:** **Data collection** Two physicians extract data from identified medical records **Statistical analysis:** X^2 & Fisher exact on categorical data and Kruskal-Wallis test for continuous variables Multivariate logistic regression **Outcomes** Risk factors for complicated pneumonia	to 3.41) **Other** 2.41 (0.68 to 8.56)	
Full citation Byington 2002 **Ref ID** **Country/ies where the study was carried out** USA **Study type** **Aim of the study** To determine if there are specific modifiable risk factors for the	**Sample size** 540 with pneumonnia • 153 with empyema • 387 without empyema **Characteristics** **Age (months):** 71 vs. 47 **Gender:** Not reported **Diagnosis:** Community acquired pneumonia **Inclusion criteria** ICD-9 code of pneumonia	**Interventions**	**Details** **Recruitment:** 1093 records identified 540 were CAP 153 with empyema **Methods:** Retrospective cohort **Statistical analysis:** X^2 & Fisher exact on categorical data Student's t-test for continuous variables **Outcome** Risk factors for empyema	**Results** **Antipyretic use:** Acetaminophen 31 (20%) vs. 188 (49%) Ibuprofen with or without acetaminophen 118 (77%) vs. 166 (43%) None 3 (2%) vs. 33 (9%) p < 0.0001 for difference between groups **Adjusted OR** • Varicella OR 14.0 (2.3 to 86.5) • Duration of fever • 1 to 6 days 2.2 (1.1 to	**Limitations** **Other information**

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
development of empyema in children **Study dates** 1 July 1993 to 1 July 1999 **Source of funding** Research grants AAP resident research grant and Robert Wood Johnson award	with or without empyema **Exclusion criteria** Viral pneumonia Hospital acquired Caused by aspiration pneumonia Cystic fibrosis Neonate			4.5) • >= 7 days 6.4 (2.9 to 13.9) • Age • 1 to 2 1.8 (0.8 to 3.7) • >= 3 4.0 (1.9 to 8.2) • Chest pain 2.4 (1.2 to 4.7) • Medication received before hospitalisation • Ibuprofen 4.0 (2.5 to 6.5) • Ceftriaxone 3.3 (1.5 to 7.1)	
Full citation Sugimura, 1994 **Ref ID** **Country/ies where the study was carried out** Japan **Study type** Prospective case control study **Aim of the study** Whether paracetamol affects the outcome of children with fever due to a bacterial fever. **Study dates** March 1992 to May 1992 **Source of funding** Not stated	**Sample size** 208 101 with pneumonia 107 controls **Characteristics** **Age:** 3.3 vs. 3.29 **Gender (males, n):** 54 vs. 55 **Temperature** 38.7C vs. 38.8C **Inclusion criteria** • Fever (=>38C) • Respiratory symptoms due to bacterial infection **Exclusion criteria** • History of asthma, convulsions or congenital heart disease. • Taken medication 3 days prior to study	**Interventions** Parents advised to give paracetamol every 6 hours as needed. Follow-up after 3 days Pneumonia defined after study as: WBC 10000/mm3, CRP + and abnormal chest findings.	**Details** **Recruitment:** Setting was Children's hospital 3060 assessed 208 met inclusion criteria 101 found to have pneumonia 107 did not have pneumonia **Methods:** No mention of ethics approval or consent No mention of sample size calculation Data recorded by parents: • Temperature four times a day • Antipyretic use **Statistical analysis:** Student t-test or Chi2 Significance set at 0.05 .	**Results** Children age 6 months to 15 years No difference in demographics between pneumonia and control cases Mean number of doses was: 2.52 +/- 0.8 in pneumonia 1.37 +/- 0.72 in controls, p < 0.001	**Limitations** Observational study design **Other information**

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
	• Diagnosed with mycoplasma infection • Bacterial UTI • Viral syndrome • Did not continue showing high temperature after 3 days of illness (=> 38*)				
Full citation Doran, 1989 **Ref ID** **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** Whether acetaminophen affects the duration or severity of childhood varicella. **Study dates** April 1984 to May 1985 **Source of funding** Robert Wood Johnson General Pediatrics Academic Development Program	**Sample size** 72 children 37 acetaminophen 31 placebo 3 did not complete the study **Characteristics** **Age:** 5.1 (+/- 2.6) vs. 5.6 (+/- 2.6) **Gender (males, n):** 13 vs. 18 **Inclusion criteria** • Children aged 1 to 12 years • With varicella • Within 36 hours of first lesions appearing **Exclusion criteria** • History of seizures or other neurologic disorders • Receiving long-term medical care • Immunosuppressed • Taken any medication within 48 hours of study	**Interventions** Acetaminophen at 10 mg/kg given 4 times daily for 4 days Placebo using same schedule	**Details** • **Recruitment:** 192 children assessed. • 82 had been ill for too long for study entry • 17 had taken medications • 9 parents refused entry • 12 ineligible for medical reasons • 72 entered study **Methods:** Randomisation using a random numbers table Subjects and investigators were blinded to allocation. Data collected by parents: temperature and symptoms for 6 days **Statistical analysis:** Sample size calculation of 60 to detect a 1 day difference in day to last vesicle formation (alpha at 0.05 and beta at 80%. Continuous variables assessed using student t-test Two-way ANOVA used to compare categorical data.	**Results** Fever present (>=38C) present in 38 children: 21 in acetaminophen and 17 in placebo No difference between groups for itching, activity, appetite or overall condition when measured for trend over time. No difference with combinations of variables. Children in placebo group were more active that acetaminophen group on day 2 ($p<0.05$), but had more itchiness on day 4 ($p<0.05$) **Time to last new vesicle** 3.9 (+/- 1.4), n = 31 days vs. 4.1 (+/- 1.2) days, n = 37. P = 0.64 **Time to total scabbing** 5.6 (+/- 2.5), n = 24 days vs. 6.7 (+/- 2.3) days, n = 34. P = 0.048 **Time to total healing**	**Limitations** • High missing data for placebo group • Small sample size, so results sensitive to change **Other information**

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
				16.1 (+/- 5.6 days), n = 28 vs. 16.2 (+/- 5.8 days), n = 36. 0.45	
Full citation Lesko, 2001 **Ref ID** **Country/ies where the study was carried out** **Study type** Prospective case-control study **Aim of the study** NSAIDs use increases the risk of invasive GAS infection, with a primary interest in necrotizing infections, in children with varicella. **Study dates** June 1996 to September 1998 **Source of funding** McNeil Consumer Healthcare	**Sample size** N = 224 52 cases of GAS 172 controls with uncomplicated varicella **Characteristics** **Mean age (months)** 58 (SD 32) vs. 62 (SD 34) **Sex male (%)** 56 vs. 62 **Inclusion criteria** **Cases** Aged less than 19 Hospitalised with necrotizing soft tissue infection or other invasive GAS infection within 2 weeks of primary varicella **Controls** Children age less than 19 Primary varicella without complications. **Exclusion criteria** Not specified	**Interventions** Children with necrotizing soft tissue infection or other invasive GAS infection compared to children with uncomplicated varicella based on medication use: • Acetaminophen alone • Ibuprofen alone • Both	**Details** **Setting** Paediatric units in Boston area of USA **Methods:** Ethical approval gained Informed consent gained from parents **Data collection** Structure interview by trained research nurse - Demographics - Symptoms within 7 days - Severity of symptoms - Medication use – timing and dose Onset of GAS based on standardised criteria. **Statistical analysis:** X2 used to compare proportions and Wilcoxon rank-sum test used for continuous variables Odd ratios used to compare use of medication and outcome. Multivariate analysis undertaken adjusting for race, household income, exposure to varicella at home and percentage of days with oral temperature > 39.4C	**Results** **Risk factors for GAS** - Race - Household income <$15k - Exposed to varicella at home - Temperature > 39.4C on 33% of days At least 1 dose of acetaminophen matched OR 1.4 (95% CI 0.69 to 2.9), multivariate 1.2 (0.5 to 3.0) At least 1 dose of ibuprofen match OR 2.9 (95% CI 2 to 6.9), multivariate 3.9 (1.3 to 12) **Mutually exclusive groups** **Intervention, case numbers, control numbers, Match OR (95% CI), Adjusted OR (95% CI)** **None,** 15, 58, 1, 1 (reference category **Acetaminophen only**, 19, 78, 0.98 (0.43 to 2.2), 0.94 (0.34 to 2.6) **Ibuprofen only,** 5, 23, 1.5 (0.44 to 5.1), 2.5 (0.58 to 11) **Both,** 13, 13, 5.0 (1.6 to	**Limitations** Observational design Retrospective recall of data Cause of effect not established **Other information**

Study details	Participants	Diagnostic evaluation	Methods	Outcomes and Results	Comments
				16), 5.6 (1.2 to 25)	

9.2 Physical and drug interventions

Review question

Effect on fever and associated symptoms of treatment with:

- Paracetamol alone or NSAIDs alone, compared with placebo and with one another
- Alternating paracetamol and NSAIDs, compared with placebo, either drug alone, and taking both at the same time
- Paracetamol and NSAIDs taken at the same time, compared with placebo, and either drug alone and either drug alone.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Beasley,R., Clayton,T., Crane,J., von,Mutius E., Lai,C.K., Montefort,S., Stewart,A., ISAAC Phase Three Study Group., Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme, Lancet, 372, 1039-1048, 2008 **Ref Id** 119194 **Country/ies where the study was carried out** Multi-national - analysis undertaken in New Zealand **Study type** Prospective cohort study **Aim of the study** Analyse association between paracetamol use and parent-reported symptoms of asthma in 6-7 year old	**Sample size** 226,248 children aged 6 to 7 from 87 centres in 34 countries collected. 205,487 children aged 6 to 7 from 73 centres in 31 countries used in analysis. 194,55 children aged 6 to 7 from 69 centres in 29 countries used in paracetamol analysis **Characteristics** Demographic information not provided. **Inclusion criteria** Parents with children aged 6 to 7 **Exclusion criteria** None	**Interventions** Questionnaire 1 on prevalence of asthma, rhinoconjunctivitis and eczema. Questionnaire 2 on environmental factors, both protection and risk-factors & demographics	**Details** **Setting** 73 centres in 31 countries. **Sampling** Random sample of schoolchildren age 6 to 7 from schools in defined geographic area. Two questionnaires completed by parents. • Questionnaire 1 on prevalence of asthma, rhinoconjunctivitis and eczema. • Questionnaire 2 on environmental factors, both protection and risk-factors & demographics **Statistical analysis** Centre had to assess at least 1000 children and have a	**Results** **Data collection** 226,248 children from 87 centres in 34 countries collected. 205,487 children from 73 centres in 31 countries used in analysis. 194,55 children from 69 centres in 29 countries used in paracetamol analysis 105,041 children from 47 centres in 20 countries used in multivariate analysis. **Association between paracetamol use and severe asthma** Variable: Adjusted ; Adjusted complete case; Multivariate analysis Paracetamol in first year: 1.82 (1.70 to 1.95); 1.82 (1.65 to 2.00); 1.43 (1.30 to 1.58) Current use = Medium vs. none: 1.31 (1.19 to 1.44); 1.44 (1.26 to 1.66); 1.33 (1.15 to 1.53)	**Limitations** Questionnaires required retrospective recall of paracetamol use and environmental exposure Questionnaires had to be translated into many languages and meaning could change. Association between paracetamol and asthma might be causative or be confounded by other factors. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
children. **Study dates** Dates not given **Source of funding** BUPA foundation, HRC New Zealand, Astra Zeneca, Glaxo Wellcome, New Zealand Lottery Board, +			response rate of 60%+ Multivariate analysis undertaken. Results adjusted for sex, region, language, and gross national income. Centres were modelled as random effects. Imputation used to demonstrate no effect of using complete case analysis. **Outcomes** paracetamol use for fever in first year of life and asthma symptoms at age 6 to 7	Current use = High vs. none: 3.92 (3.56 to 4.32); 4.23 (3.65 to 4.91); 3.54 (3.05 to 4.11) **Association between paracetamol and...** Adjusted Medium vs. 0 / High vs. 0 Asthma: 1.55 (1.46 to 1.65) / 3.45 (3.22 to 3.69) Rhinoconjunctivitis: 1.37 (1.28 to 1.45) / 2.85 (2.65 to 3.06) Eczema: 1.26 (1.18 to 1.33) / 1.94 (1.81 to 2.07) Adjusted with complete covariates Medium vs. 0 / High vs. 0 Asthma: 1.74 (1.58 / 3.73 (3.35	

Study details	Participants	Interventions	Methods	Outcomes and Results			Comments
					to 1.91)	to 4.14)	
				Rhinoconjunctivitis	1.42 (1.29 to 1.56)	3.11 (2.79 to 3.47)	
				Eczema	1.25 (1.14 to 1.67)	2.05 (1.85 to 2.28)	
					Multivariate analysis		
					Medium vs. 0	High vs. 0	
				Asthma	1.61 (1.46 to 1.77)	3.23 (2.91 to 3.60)	
				Rhinoconjunctivitis	1.32 (1.20 to 1.46)	2.81 (2.52 to 3.14)	
				Eczema	1.18 (1.08 to 1.30)	1.87 (1.68 to 2.08)	
Full citation	**Sample size**	**Interventions**	**Details**	**Results**			**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Gupta,H., Shah,D., Gupta,P., Sharma,K.K., Role of paracetamol in treatment of childhood Fever: a double-blind randomized placebo controlled trial, Indian Pediatrics, 44, 903-911, 2007 **Ref Id** 119208 **Country/ies where the study was carried out** India **Study type** RCT **Aim of the study** Hypotheses that (1) Use of paracetamol prolongs the fever clearance time (2) the rate of fall of temperature following paracetamol administration is similar to placebo. **Study dates** Not stated **Source of funding** No funding received	954 eligible children 210 randomised - 103 to paracetamol - 107 to placebo **Characteristics** Paracetamol vs. placebo Age (months): 26.1 (+/- 16.9), 27.1 (+/- 17.1) Weight (kg): 11.5 (+/- 3.1), 11.8 (+/- 3.1) Duration of illness (hours): 38.3 (+/- 21.8), 41.4 (+/- 22.9) Duration of fever (hours): 20.1 (+/- 12.4), 21.7 (+/- 13.0) Sex (M:F): 1.34 to 1, 0.91 to 1 Diagnosis: URTI: 55 vs. 57 Pneumonia: 24 vs. 24 WRTI: 24 vs. 26 **Inclusion criteria** Children aged 6 months to 6	Liquid paracetamol at 15mg/kg. Dose repeated if child vomit within 15 minutes of administration or 6 hours if axillary temperature was >= 37.6C Placebo In-hospital rescue therapy of ibuprofen and/or sponging given if the child's temperature was >40.5C. Parents asked not to use other therapies at home, such as sponging.	**Setting:** Tertiary care hospital **Recruitment** Ethics approval obtained Informed consent obtained **Allocation** Randomisation using number tables and coded bottles. Randomisation undertaken at pharmacy. Investigators and participants were blinded to allocation **Data collection** Temperature recorded axillary at 0, 30 minutes and hourly until 6 hours by an investigator Home monitoring undertaken by parents using pre-standardised thermometer at 6 hourly intervals. Subjective improvement was	Temperature (C (SD)) paracetamol vs. placebo 1 Hour - 38.7 (0.9) vs. 38.4 (1.0) 2 hours - 38.6 (0.9) vs. 38.0 (0.8) 3 hours - 38.55 (1.0) vs. 37.8 (0.80 4 hours - 38.0 (1.0) vs. 37.6 (0.8) 5 hours - 38.4 (0.9) vs. 37.6 (0.7) 6 hours - 38.3 (1.0) vs. 37.7 (0.7) Quality of life - at least 1 category improvement from baseline Activity • 4 hours: 29 vs. 4 • 6 hours: 62 vs. 17 Alertness • 4 hours: 22 vs. 4 • 6 hours: 60 vs. 22 Comfort • 4 hours: 19 vs. 9 • 6 hours: 38 vs. 8 Mood	Temperature measurements taken from graph. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	years Temperature between 37.6C to 40.5C Duration of illness less than 2 days Diagnosis of uncomplicated respiratory tract infection. **Exclusion criteria** Personal or family history of seizures, neurological, hepatic or renal disease, peptic ulcer, tuberculosis, blood dyscrasia, maligancy or immune suppression. Known hypersensitivity to NSAIDs Administration of antipyretics or antibiotics within 2 days		noted during first 6 hours for activity, alertness, mood, comfort, appetite and fluid intake using a 5 point Likert scale. Adverse events were recorded. **Outcomes** Fever clearance time (< 37.5C) - Primary outcome Rate of fall in temperature Percentage reduction in temperature Proportion of afebrile patients Symptomatic improvement Adverse events **Statistics** Sample size calculation of 84 per group to detect 12 hour difference in clearance of fever a p = 0.05 and power = 90% Rate of fall assessed using MANOVA Means compared using t-test or ANOVA Proportions analysed using Chi2	• 4 hours: 11 vs. 3 • 6 hours: 37 vs. 13 Appetite • 4 hours: 7 vs. 1 • 6 hours: 21 vs. 1 Fluid intake • 4 hours: 3 vs. 2 • 6 hours: 23 vs. 2	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kramer,L.C., Richards,P.A., Thompson,A.M., Harper,D.P., Fairchok,M.P., Alternating antipyretics: antipyretic efficacy of acetaminophen versus acetaminophen alternated with ibuprofen in children, Clinical Pediatrics, 47, 907-911, 2008 **Ref Id** 119220 **Country/ies where the study was carried out** USA **Study type** Randomised, prospective, double-blind, placebo-controlled trial **Aim of the study** Antipyretic efficacy of alternating acetaminophen with ibuprofen versus acetaminophen **Study dates** January 2004 to January 2006 **Source of funding** Resident Research Grant from the American Academy of Pediatrics	**Sample size** 42 asked about participation 40 agreed to join after further information and were randomised 38 met inclusion criteria; 2 were excluded as temperature did not meet inclusion criteria 36 had complete data; 2 from the alternating group had one temperature data point missing. **Characteristics** **Variable, Acetaminophen (n = 19), Acetaminophen and Ibuprofen (n = 19)** Male gender (n, %): 9 (52.6%), 9 (52.6%) Mean Age (months): 33.6, 32.0 Diagnosis bacterial: 6 (31.6%), 7 (36.8%) Antimicrobial prescription: 6 vs. 9 **Inclusion criteria**	**Interventions** Treatment schedules based on commonly recommended regimens. **Group A** 0 hours - Acetaminophen (15 mg/kg) 3 hours - placebo (matching Ibuprofen) 4 hours - Acetaminophen (15 mg/kg) **Group B** 0 hours - Acetaminophen (15 mg/kg) 3 hours - Ibuprofen (10 mg/kg) 4 hours - Acetaminophen (15 mg/kg)	**Details** **Study design** Informed consent obtained Computer generated randomisation blocks Pharmaceuticals were dispensed by a third-party unblinded pharmacist. Sample size calculation reported 16 subjects per arm at 80% power and 5% difference to detect difference of 0.6C **Setting** Pediatric Clinic at Madigan Army Medical Center **Statistical methods** Univariate analysis between groups on mean temperature, symptoms and caretaker perception using Fisher exact test. **Outcomes** Outcomes reported by caretaker Temperature recorded at baseline, 3, 4, 5, and 6 hours.	**Results** **Variable, Acetaminophen (n = 19), Acetaminophen and Ibuprofen (n = 19)** Hour 0: 38.8 (38.6 to 39.0), 39.2 (38.8 to 39.6), NS Hour 3: 37.7 (37.5 to 37.9), 37.7 (37.4 to 38.0), NS Hour 4: 38.0 (37.5 to 38.5), 37.4 (37.0 to 37.8), 0.05 Hour 5: 37.9 (37.5 to 38.3), 37.1 (36.8 to 37.4), 0.003 Hour 6: 37.5 (37.1 to 37.9), 37.4 (37.0 to 37.8), NS Would need more antipyretics at 3 hours: 39%, 21% Would need more antipyretics at 4 hours: 33%, 21% 8 children across groups reported symptoms, but none stopped treatment	**Limitations** Temperature was recorded by caretaker rather than trained clinician Temperature was measured differently by age of child **Other information** **Further limitations** Stated that it is a placebo controlled trial, but no true placebo arm is used. Instead, acetaminophen and placebo are used in one arm, and the effect of acetaminophen is likely to continue into the placebo period. Also, no analysis provided of placebo period. No caretakers in acetaminophen group gave OTC antipyretics vs. 4 in the alternating group (p= 0.04). Sample size difference is not

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Fever above 38C Fever main complaint **Exclusion criteria** History of antipyretic use within previous 4 hours Known allergy or other contraindications to medications		Temperature measured using digital thermometer. Orally in children older than 2 and rectally for children less than 2 years. Symptom survey Belief of need for additional antipyretics.		justified by authors Children older than 5 were included in the study population **Author conclusion** Significant temperature difference in favour of alternating, but parents did not perceive any difference between treatments.
Full citation Nabulsi,M.M., Tamim,H., Mahfoud,Z., Itani,M., Sabra,R., Chamseddine,F., Mikati,M., Alternating ibuprofen and acetaminophen in the treatment of febrile children: a pilot study [ISRCTN30487061], BMC Medicine, 4, 4-, 2006 **Ref Id** 119228 **Country/ies where the study was carried out** Lebanon **Study type** Randomised, double-blind and placebo-	**Sample size** n=70 **Characteristics** INTERVENTION GROUP- IBUPROFEN AND ACETAMINOPHEN Mean age in years (SD): 3.7 (3.3) Mean weight in kg (range): Not reported Sex (%): Male 26 (70.3%) Female 11 (29.7%) Diagnosis: Viral (70.3%) Bacterial (21.6%) Other (8.1%)	**Interventions** INTERVENTION GROUP n=37 Ibuprofen 10mg/kg, followed by acetaminophen 15mg/kg at 4h CONTROL GROUP n=33 Ibuprofen 10mg/kg, followed by placebo at 4h	**Details** Treatment regimen -Administration of acetaminophen or placebo 4 hours after baseline chosen to coincide with the expected time of maximum antipyresis of ibuprofen, after which there is gradual waning of this effect. Sample size calculation -50% of febrile subjects who receive ibuprofen and placebo will drop their rectal temperature to <38.0^{o}C at 6 hours, and 80% of subjects in the combination antipyretic group will become afebrile at 6 hours. To detect this 30% difference in the proportions of afebrile subjects, at the 2-sided	**Results** Afebrile at 6 hours, N (%) Combined ibuprofen and acetaminophen: n=30 (83.3) Ibuprofen: n=19 (57.6) P value: 0.018 Afebrile at 7 hours, N (%) Combined ibuprofen and acetaminophen: n=31 (86.1) Ibuprofen: n=14 (45.2) P value: <0.001 Afebrile at 8 hours, N (%) Combined ibuprofen and	**Limitations** -Though results suggest superiority of the combined regimen, findings need to be confirmed as the trial was forced to stop (due to obstacles facing recruitment e.g.: parental anxiety regarding children's participation in research and physician's reluctance to permit enrolment of their patients in a clinical trial) before achieving the calculated sample size.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
controlled trial **Aim of the study** To compare the antipyretic effectiveness and safety of a single administration of alternating ibuprofen and acetaminophen doses to that of ibuprofen mono-therapy in febrile children. **Study dates** November 2002-April 2005 **Source of funding** Funded by the Medical Practice Plan of the Faculty of Medicine at the American University of Beirut, Grant number 686056	Mean temperature at baseline (SD): 39.3 (0.5) CONTROL GROUP-IBUPROFEN AND PLACEBO Mean age in years (range): 3.6 (2.9) Mean weight in kg (range): Not reported Sex (%): Male 19 (57.6%) Female 14 (42.4%) Diagnosis: Viral (54.5%) Bacterial (33.3%) Other (12.1%) Mean temperature at baseline (SD): 39.4 (0.6) **Inclusion criteria** -Febrile inpatients aged between 6 months and 14 years -Rectal temperature >/=38.8C **Exclusion criteria** Children with: -Vomiting -Any medical or surgical condition that precluded oral drug administration		5% level, a sample size of 90 subjects is needed: 45 in each group. Definition and measurement of fever -Fever was defined as rectal temperature >/=38.8^{o}C -Baseline rectal temperature was recorded using a portable thermistor with single-use disposable probe covers. Rectal temperatures were recorded by the nurse in charge at 4, 5, 6, 7 and 8 hours from baseline. Outcome measurement -Primary outcome: proportion of children with normal body temperature at 6 hours (defined as a rectal temperature between 36.5^{o}C and 37.9^{o}C). -Additional outcomes: *Proportions of afebrile children in each group at 7 and 8 hours from baseline *Maximum decline in temperature during the study period *Time to recurrence of fever *The mean temperature changes from baseline at t=4,5,6,7 and 8 hours *The proportion of patients in each group with any adverse effect that may be related to either drug such as	acetaminophen: n=29 (80.6) Ibuprofen: n=11 (35.5) P value: <0.001 -Logistic regression revealed that the intervention group were significantly more likely than the control group to become afebrile at 6,7 and 8 hours: OR(95%CI): 5.6 (1.3,23.8) at 6 hours; 19.5(3.5,108.9) at 7 hours and 15.3(3.4-68.3) at 8 hours Maximum temperature decline Mean (SD) Combined ibuprofen and acetaminophen: 2.2 (0.7) Ibuprofen: 2.1 (1.2) P value: 0.793 Time to recurrence of fever -The combined antipyretic group had a significantly longer duration of antipyresis than the control group with the mean (SD) times to recurrence of fever being 7.4 (1.3) hours versus 5.7 (2.3) hours, respectively; P<0.001 Adverse events -Low body temperature defined as rectal temperature below 36.5^{o}C occurred in 5 subjects (13.9%) in the combined antipyretic group and 6(18.2%) in the control group (P=0.6)	-Indirect population as children aged from 6 months to 14 years **Other information** -Children with concurrent or previous intake of antibiotics were not excluded if still febrile at the time of interview. All antipyretics were stopped for 8 hours prior to the initiation of the study. -Subjects were inpatients of the American University of Beirut Medical Centre (AUBMC) a tertiary care facility, and Najar Hospital, a secondary care facility.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	-Acute or chronic hepatic disease -Malabsorption syndromes -Acute or chronic renal disease with the exception of urinary tract infection -Chronic metabolic disease -Bleeding disorders -Asthma -Chronic neurological disease that may affect central thermoregulation -Cancer -Immune suppression -Sepsis -Critical medical status -Known allergy to acetaminophen or ibuprofen		hypothermia, chilliness or gastrointestinal bleeding Intention to treat analysis -Intent to treat analysis (method not reported). Other information -Children were assigned a random number by the hospital pharmacist according to a computer-generated random number list. The pharmacist who prepared all medications was unblinded to treatment allocations. -Informed consent obtained		
Full citation Pierce,C.A., Voss,B., Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. [93 refs], Annals of Pharmacotherapy, 44, 489-506, 2010 **Ref Id** 119230 **Country/ies where the study was**	**Sample size** 26 studies were included, the sample size in the studies ranged from 22 – 419 children. **Characteristics** Participants' age ranged between 6 months to 18	**Interventions** Direct comparison of ibuprofen and acetaminophen. Paediatric pain: ibuprofen dosages ranging from 7.5mg/kg to 20mg/kg or 200 mg to 400 mg one to four times a day; acetaminophen	**Details** Recruitment: Paediatric pain: 18 studies contained data for the direct comparison of ibuprofen and acetaminophen on the effect on pain; only 6 studies were CRT and contained sufficient information to compute as standard mean difference (SMD). Paediatric fever:	**Results** Paediatric pain: standard mean difference of pain measurement for acetaminophen versus ibuprofen in children was 0.28; 95% CI 0.10 to 0.46) at 2 hours post-dose. Paediatric fever: standard mean difference of fever for acetaminophen versus ibuprofen in children was 0.26; 95% CI 0.10 to 0.41) at 2 hours post-dose.	**Limitations** The paediatric included children older than 5 years of age. Some patients over the age of 18 were included. No clear information was reposted for the numbers of children

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
carried out NA **Study type** Meta-Analysis and qualitative review. **Aim of the study** To evaluate the analgesic and antipyretic efficacy and safety of ibuprofen and acetaminophen in children and adults. **Study dates** Literature searches were performed using PubMed/MEDLINE (through August 2009) and EMBASE (through January 2008). **Source of funding** Not reported.	years. **Inclusion criteria** Clinical trials included prospective and retrospective studies that provided efficacy and/or safety data for the direct comparison of ibuprofen and acetaminophen. The articles were classified to contain efficacy data, safety data or both. The articles containing efficacy data were limited to studies including : 1) Direct comparison of ibuprofen and the 4-h point was selected for the early evaluation of acetaminophen in the treatment of fever and /or pain 2) The dose and 3) The method of pain and/or fever measurement. The articles containing safety data were limited to studies in which safety or tolerability of ibuprofen and acetaminophen was directly compared in term of adverse events (AE). **Exclusion criteria** The study were eluded if either the ibuprofen or acetaminophen were given in concomitance to other medication such us codeine,	ranging from 10mg/kg to 40mg/kg or 360 to 650 mg one to four times a day. <u>Paediatric fever:</u> ibuprofen dosages ranging from 0.5mg/kg to 20mg/kg or 50 mg to 200 mg one to four times a day; acetaminophen ranging from 8mg/kg to 50mg/kg or125 to 500 mg one to four times a day. <u>Paediatric adverse events:</u> Not reported	30 studies contained data for the direct comparison of ibuprofen and acetaminophen on the effect on fever; only 7 studies were CRT and contained sufficient information to compute as standard mean difference (SMD). <u>Paediatric adverse events:</u> 31 studies contained data for the direct comparison of ibuprofen and acetaminophen on the adverse events; only 19 studies were CRT and contained sufficient information to compute as standard mean difference (SMD). <u>Methods:</u> Meta-analyses on the subset of randomized clinical trial articles that reported sufficient quantitative information to calculate standardized mean difference (pain and fever)were used. The data were separated in adult and paediatric data, the paediatric studies were studies including a population age lower than 18years. For the meta-analyses, only studies that were explicitly noted to be RCT with both interventions were included. <u>Paediatric pain:</u> Pain was measured for example using visual analogue scale (VAS) and ordinal scale ant an early time of 2 h post dose was utilised (if possible) <u>Paediatric fever:</u> How fever was measured was not reported, the 4-h time point	<u>Paediatric adverse events:</u> the combined estimated of the odds ratio comparing proportion of children experiencing at least one adverse events for acetaminophen versus ibuprofen in children was 0.82; 95% CI 0.60 to 1.12)	involved in wash arm of the studies. The methods used to measure temperature and pain was not clearly reported. The dose used and the timing was not clearly reported. **Other information** Pain and fever were defined by the authors of each individual study.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	other opioids, or other analgesic/antipyretics.		was selected for the early evaluation. Intervention: Direct comparison of ibuprofen and acetaminophen with different dosages and time of administration. Statistical analysis: Forest plots were created to provide al summary of the study-specific and combined log-amended odds ratios. For continuous measurements of temperature and pain VAS scores, the standardised mean difference was computed for each study all measurement times as the acetaminophen mean minus the ibuprofen mean, provided sufficient information was reported.		
Full citation Sarrell,E.M., Wielunsky,E., Cohen,H.A., Antipyretic treatment in young children with fever: acetaminophen, ibuprofen, or both alternating in a randomized, double-blind study, Archives of Pediatrics and Adolescent Medicine, 160, 197-202, 2006 **Ref Id** 119236 **Country/ies where the study was carried out** Israel **Study type** Randomised, double-blind, parallel-	**Sample size** n=464 **Characteristics** GROUP A: ACETAMINOPHEN Age, mo (SD): 18.6 (8.72) Mean weight in kg (range): Not reported Sex (%): Male 71 (46%) Female 83 (54%) Diagnosis: URI (43%) Acute otitis media (10%) Pharyngitis (7%) Bronchiolitis	**Interventions** GROUP A -n=154 -Acetaminophen 12.5mg/kg per dose every 6 hours; maximum 50mg/kg per day GROUP B -n=155 -Ibuprofen 5mg/kg per dose every 8 hours; maximum 20mg/kg per day GROUP C -n=155	**Details** Treatment regimen -Group A: One half of the group received initial loading with acetaminophen (25mg/kg) and the other half received initial loading with ibuprofen (10mg/kg) -Group B: One half of the group received initial loading with acetaminophen (25mg/kg) and the other half received initial loading with ibuprofen (10mg/kg) -Group C: One half of the group received initial loading with acetaminophen (25mg/kg) and the other half received initial loading with ibuprofen	**Results** FEVER Admission Acetaminophen (Group A), mean +/- SD(95%CI): 40.74 +/- 1.01 (40.58-40.90) Ibuprofen (Group B), mean +/- SD(95%CI): 40.58 +/- 1.02 (40.42-40.74) Acetaminophen and Ibuprofen (Group C), mean +/-SD (95%CI): 40.71 +/- 0.93 (40.56-40.86) P=0.31 Day 1 Acetaminophen (Group A), mean +/- SD(95%CI): 40.55 +/- 1.31 (40.34-40.76) Ibuprofen (Group B), mean +/- SD(95%CI): 40.6 +/- 1.46 (40.37-40.83)	**Limitations** -Daily temperature was recorded by parents instead of trained clinicians so inaccuracies possible. **Other information** -Subjects were from 3 primary paediatric community centres, 2 urban and 1 rural in central Israel.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
group trial **Aim of the study** To compare the clinical effectiveness of acetaminophen and ibuprofen alone with an alternating regimen of both drugs in reducing fever and stress signs in infants and young children. **Study dates** September 15 2003-March 15 2004 **Source of funding** Not reported	(5%) Gastroenteritis (5%) Viral illness (30%) Mean temperature at baseline (SD): Not reported <u>GROUP B: IBUPROFEN</u> Age, mo (SD): 19.5 (9.09) Mean weight in kg (range): Not reported Sex (%): Male 73 (40%) Female 82 (60%) Diagnosis: URI (52%) Acute otitis media (8%) Pharyngitis (5%) Bronchiolitis (5%) Gastroenteritis (5%) Viral illness (25%) Mean temperature at baseline (SD): Not reported <u>GROUP C: ACETAMINOPHEN AND IBUPROFEN</u> Age, mo (SD): 19.3 (9.29) Mean weight in kg (range): Not reported Sex (%): Male 62 (38%) Female 93 (62%) Diagnosis: URI (51%) Acute otitis media (11%) Pharyngitis (2%) Bronchiolitis (6%) Gastroenteritis (4%) Viral illness (26%)	-Acetaminophen 12.5mg/kg per dose; maximum 50mg/kg per day alternating with ibuprofen 5mg/kg per dose; maximum 20mg/kg per day every 4 hours	(10mg/kg) -The infant was then given the loading dose from bottles marked A or B by a second nurse. <u>Sample size calculation</u> -Based on a double-blind clinical trial of 2 study populations of febrile children assigned randomly to receive acetaminophen or ibuprofen. Since the study found no significant difference between the groups in the decrease in fever, variations in irritability score was used for sample size calculation. <u>Definition and measurement of fever</u> -Fever was defined as rectal temperature >/=38.4C -Temperature at admission measured by admitting nurse. -Child's rectal temperature measured by parents using a glass and mercury rectal thermometer 3 times daily during treatment and once daily for another 10 days. <u>Outcome measurement</u> -Primary outcome measures: admission fever, admission NCCPC score (level of distress) and amount of	Acetaminophen and Ibuprofen (Group C), mean +/-SD (95%CI): 39.64 +/- 1.17 (39.45-39.82) P<0.001 <u>Day 2</u> Acetaminophen (Group A), mean +/-SD(95%CI): 39.74 +/- 1.37 (39.51-39.95) Ibuprofen (Group B), mean +/-SD(95%CI): 39.66 +/- 1.48 (39.42-39.89) Acetaminophen and Ibuprofen (Group C), mean +/-SD (95%CI): 38.78 +/- 0.87 (38.64-38.92) P<0.001 <u>Day 3</u> Acetaminophen (Group A), mean +/-SD(95%CI): 39.34 +/- 1.19 (39.15-39.53) Ibuprofen (Group B), mean +/-SD(95%CI): 39.64 +/- 1.46 (39.41-39.87) Acetaminophen and Ibuprofen (Group C), mean +/-SD (95%CI): 38.54 +/- 0.74 (38.42-38.66) P<0.001 <u>NCCPC Admission</u> Acetaminophen (Group A), mean +/-SD(95%CI): 18.30 +/- 1.67 (18.03-18.56) Ibuprofen (Group B), mean +/-SD(95%CI): 19.00 +/- 1.27 (18.80-19.20) Acetaminophen and Ibuprofen (Group C), mean +/-SD (95%CI): 19.46 +/- 2.40 (19.08-19.84) P<0.001 <u>Day 1</u>	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Mean temperature at baseline (SD): Not reported **Inclusion criteria** -Children aged 6-36 months -Rectal temperature of at least 38.4C **Exclusion criteria** -Children who were not attending day care centres -Children who had taken any temperature-altering drugs or antibiotics within 10 days before presentation -Children with known abnormal liver or renal laboratory values -Children with medical history of: renal or hepatic impairment, gastrointestinal bleeding, known allergy to any antipyretic, congenital or acquired immunodeficiency, Reye syndrome, asthma, bronchiolitis, or malignancy -Children whose caregivers were unable to apply the Non-communicating Children's Pain Checklist (NCCPC) to measure stress		antipyretic used at the 3-day time point -Secondary outcome measures: recurrence of fever within 5 and 10 days after initiation of treatment, total days absent from day care, number of emergency department visits, hepatic and renal functions. <u>Intention to treat analysis</u> -Not reported <u>Other information</u> -A computerized random-number generator was used to stratify children according to paediatric centre in blocks of 60 numbers so that each block comprised 20 patients randomly assigned to each treatment group. -All medication bottles were distributed by the pharmacist. A list of patients and medications was kept with the pharmacist in a sealed envelope in the event of an emergency. -Informed consent was obtained.	Acetaminophen (Group A), mean +/-SD(95%CI): 11.77 +/- 2.64 (11.35-12.19) Ibuprofen (Group B), mean +/-SD(95%CI): 11.48 +/- 2.58 (11.07-11.89) Acetaminophen and Ibuprofen (Group C), mean +/-SD (95%CI): 9.26 +/- 2.49 (8.86-9.65) P<0.001 <u>Day 2</u> Acetaminophen (Group A), mean +/-SD(95%CI): 8.87 +/- 2.54 (8.47-9.27) Ibuprofen (Group B), mean +/-SD(95%CI): 8.83 +/-2.67 (8.40-9.25) Acetaminophen and Ibuprofen (Group C), mean +/-SD (95%CI): 5.09 +/-2.78 (4.65-5.53) P<0.001 <u>Day 3</u> Acetaminophen (Group A), mean +/-SD(95%CI): 7.66 +/- 2.96 (7.19-8.13) Ibuprofen (Group B), mean +/-SD(95%CI): 7.96 +/- 2.71 (7.53-8.39) Acetaminophen and Ibuprofen (Group C), mean +/-SD (95%CI): 4.18+/-2.74 (3.75-4.62) P<0.001 <u>Adverse events</u> None of the patients in any of the groups had a drug related adverse event or serious illness.	
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Southey,E.R., Soares-Weiser,K., Kleijnen,J., Systematic review and meta-analysis of the clinical safety and tolerability of ibuprofen compared with paracetamol in paediatric pain and fever. [77 refs], Current Medical Research and Opinion, 25, 2207-2222, 2009 **Ref Id** 119237 **Country/ies where the study was carried out** UK **Study type** Meta-analysis of RCTs **Aim of the study** To compare the tolerability and safety between ibuprofen and paracetamol when used as antipyretic and analgesic agents in children from 0 to 18 years of age. **Study dates** Studies undertaken between 1950 to 2008 **Source of funding** Commercially funded by Reckitt Benckiser	5517 studies identified, 462 articles ordered and 36 included in review. **Characteristics** All studies were classified as RCTs **Inclusion criteria** RCT comparing efficacy or tolerability and safety of ibuprofen or paracetamol with placebo. Controlled observational studies for rare AEs Case-series of more than 1000 participants Children up to the age of 18 years of age who have pain and/or fever **Exclusion criteria** Not reported	Paracetamol or Ibuprofen used to treat paediatric pain or fever	Systematic review Search undertaken on Medline, Embase, The Cochrane library, ACP Journal Club, and Pascal for all years until 2007. Studies included that: • RCTs, controlled observational studies, case-series with 1000+ participants • Included children aged up to 18 • Treated for pain or fever • Reported on adverse events Meta-analysis using RevMan Dichotomous variables assessed using RR Continuous variables assessed using WMD	**Systemic reactions with ibuprofen compared to paracetamol** 18 RCTs included. Ibuprofen 2937 events in 21305 patients Paracetamol 1466 events in 11164 patients RR 1.03 (95% CI 0.98 to 1.10) **Systemic reactions with ibuprofen compared to placebo** 4 RCTs Ibuprofen 38 events in 234 patients Placebo 25 events in 229 patients RR 1.39 (0.92 to 2.10) **Systemic reactions with paracetamol compared to placebo** 4 RCTs Paracetamol 16 events in 297 patients Placebo 10 events in 297 patients	Different treatment regimens used and different patient populations included. **Other information** Results dominated results by Ashraf (1999) , n = 20111. It is unclear at which level randomisation took place - the individual or the treatment unit.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				RR 1.57 (0.74 to 3.33)	
Full citation utret-Leca,E., Gibb,I.A., Goulder,M.A., Ibuprofen versus paracetamol in pediatric fever: objective and subjective findings from a randomized, blinded study, Current Medical Research and Opinion, 23, 2205-2211, 2007 **Ref Id** 119244 **Country/ies where the study was carried out** France **Study type** Double-blind double-dummy, parallel groups CRT. **Aim of the study** The main objective of this study was to compare the single-dose efficacy of 15 mg/kg paracetamol (acetaminophen) versus 10 mg/kg ibuprofen in a general practice setting. **Study dates** Not reported. **Source of funding** Funded by Boots Healthcare International.	**Sample size** A total of 304 children were enrolled. **Characteristics** <u>Ibuprofen group:</u> n = 151 Mean age ± SD= 3.84±2.78 (0.4 to 11) years Mean body weight ±SD = 17.54±7.96 (6.2 to 84.1) kg Sex (male, female) = 48.3%, 51.7% Initial tympanic temperature between 38.5 – 40.5^{o}C Diagnosis: various pathologies such us sore throat, influenza, TRI, ear infection and immunization. <u>Paracetamol group:</u> n = 150 Mean age ± SD= 3.71±2.71 (0.4 to 11) years Mean body weight ±SD = 17.58±8.97 (6.2 to 84.1) kg Sex (male, female) n = 52.0%, 48% Initial tympanic temperature between 38.5 – 40.5^{o}C Diagnosis: various pathologies such us sore throat, influenza, TRI, ear infection and immunization. **Inclusion criteria**	**Interventions** <u>Ibuprofen group:</u> ibuprofen 10mg/kg oral suspension plus paracetamol placebo <u>Paracetamol group</u>: paracetamol 15mg/kg oral suspension Ibuprofen plus a placebo.	**Details** <u>Recruitment:</u> 304 patients were enrolled. 1 was prescribed ibuprofen and 2 had a no post-baseline assessment, therefore the intent-to-treat (ITT) population was 301. The per-protocol (PP) population contained 288 children (6 children contravened the protocol by receiving the second dose of medication within the 6hours from the first dose and 7 received prohibited medication during the trial). <u>Methods:</u> The children received the medication on a random double-blind basis, received ibuprofen in the open-label phase, while who received paracetamol continued with paracetamol. The allocation to a treatment was performed using a dynamic computerized interactive voice response system (IVRS). The IVRS was also used to calculate the volumes of each study medication to be administered to that patient. The first dose of the study medication was given at the presentation. The child's tympanic temperature was taken by 30 min after the first dose of medication and then 2, 3, 4, 5, 6 and 8 hours after the dose	**Results** <u>Area under the temperature reduction curve from 0 to 6 hours</u> (mean ± SD) Ibuprofen group = -7.77± 3.54^{o}C; Paracetamol group = -7.66± 3.76^{o}C; p-value = 0.82. <u>Parents perception after first dose:</u> <u>Parents' overall opinion of the treatment:</u> Ibuprofen group = 59.2 %; Paracetamol group = 37.2%; p-value = <0.001. <u>If your child develops a fever in the future would you give him/her the same treatment?</u> Ibuprofen group = 96.5 %; Paracetamol group = 88.8%; p-value = 0.018. <u>Adverse events:</u> Ibuprofen group = 17 (11.2 %); Paracetamol group = 16 (10.6%); *p-value* = not reported.	**Limitations** <u>Not sure about the blinding</u> Children older than 5. **Other information** A subgroup analysis was performed according to age and baseline temperature there was not a statistical difference (trend in favour of Ibuprofen in both cases in children younger than 3 years and in children with baseline temperature higher then 39^{o}C). The data on parents' perception at the end of study was the same as after the first dose.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Children from the age of 3 months to 12 years with a fever of non-serious origin, only children requiring treatment on an outpatient basis were recruited. Tympanic temperature between 38.5 – 40.5^{o}C. **Exclusion criteria** Hypersensitivity at any of the drug constituents or fructose. history of any condition that interfered with the absorption of the drug, metabolism or excretion; history of asthma; angioedema; urticaria; bronchospasm or rhinitis related to treatment with NSAIDs, aspirin or paracetamol; history of peptic or duodenal ulcers or gastrointestinal bleed; severe hyperthermia with neurologic and/or hemodynamic disorder; sever hepatic failure; sever renal failure; sever heart failure; bilateral acute otitis media; systemic lupus erythematosus; confirmed or suspected infection with varicella. Children who had received treatment with antipyretic drugs up to 6 hours before inclusion or treatment with antibiotics therapy in the 12 hours before the start of the trial were also excluded.		administration of until a second dose was required. The second and subsequent doses were administered open-label for up to 3 days by parents at home. Parents were asked to response to the following global assessment questioner before administering a second dose: 1) Parents' overall opinion of the treatment: a) Very efficacious b) Efficacious c) Slightly efficacious d) Not efficacious 2) If your child develops a fever in the future would you give him/her the same treatment? The parents were asked to make an appointment to follow-up visit once the febrile episode was over. At the second visit the physical examination was conducted and parents were asked again to response to the questioner. The parents' global assessment of treatment was recorded. <u>Intervention:</u> The patients received ibuprofen 10mg/kg oral suspension plus a paracetamol placebo or paracetamol 15mg/kg oral suspension Ibuprofen plus a placebo. The first dose was administrated by the parent in the outpatient centre and the child's tympanic temperature was taken by the		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			parents 30 min after the medication. A second dose of medication was given to only if the child's temperature was equal or higher of 38.5^{o}C and least 6 hours has passed from the first dose. If the child was distress the parent could contact the investigators, which could make the decision to allow a second dose before the 6 hours but not before 4 hours from the first dose (max daily doses allowed was 3 for ibuprofen and 4 for paracetamol). Statistical analysis: Assuming a variable of 0.9^{o}C in temperature reduction, a minimum of 140 children per group were required in order to demonstrate a difference of 0.35^{o}C for temperature reduction between the two treatments with 90% power.		
Full citation Hay,A.D., Redmond,N.M., Costelloe,C., Montgomery,A.A., Fletcher,M., Hollinghurst,S., Peters,T.J., Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial, Health Technology Assessment (Winchester, England), 13, 1-163, 2009 **Ref Id** 139274 **Country/ies where the study was**	**Sample size** 4515 contacts made across 35 sites in Bristol, UK 3477 ineligible (89%) insufficient fever 882 declined or missed 156 randomised to one of 3 groups. **Characteristics**	**Interventions** Paracetamol alone (15mg/kg) every 4 to 6 hours (maximum 4 doses in 24 hours) and/or Ibuprofen alone (10mg/kg) every 6 to 8 hours (maximum of 3 doses in 24 hours) and/or	**Details** **Study Design** Written informed consent gained from parents of children Randomisation via remote automated service to one of three groups. Groups minimised for age, severity of fever, discomfort, duration of fever, and current antibiotic use.	**Results** **Variable: paracetamol alone (n = 52), ibuprofen alone (n = 52), paracetamol plus ibuprofen (n = 52)** (Mean temperatures at time points not reported.) **Primary outcomes** Mean (SD time without fever in first 4 hours (minutes): 116.2 (65.0), 156.0 (57.6), 171.1 (40.8)	**Limitations** Sample size recalculated due to poor recruitment. 1. No placebo group, so no information on if to use antipyretics or not 2. Sample size no large enough to detect pre-specified difference between

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
carried out UK **Study type** Randomised controlled trial **Aim of the study** To investigate whether paracetamol plus ibuprofen are superior to either drug alone for increasing time without fever and the relief of fever associated discomfort in febrile children managed at home **Study dates** January 2005 to May 2007 **Source of funding** NIHR grant. No conflicts of interest.	**Variable: paracetamol alone (n = 52), ibuprofen alone (n = 52), paracetamol plus ibuprofen (n = 52)** Gender male: 26, 37, 25 Mean (SD) weight (kg): 13.0 (4.2), 13.4 (3.9), 12.6 (3.3) Mean (SD) age (months): 28.7 (17.7), 28.1 (17.4), 25.1 (13.4) Age (months) 6 to 17: 20, 18, 19 Mean (SD) temperature (C): 38.6 (0.6), 38.6 (0.6), 38.6 (0.6) Temperature <39: 37, 37, 39 Fever duration (hours) <=24: 18, 19, 19 Antibiotics use - yes: 14, 15, 17 Paracetamol use 4 to 6 hours before randomisation - yes: 20, 17, 20 Ibuprofen use 6 to 8 hours before randomisation - yes: 4, 2, 3 <u>Discomfort:</u>	matched placebo First dose given in presence of research nurse. At 48 hours drugs were retrieved and parents told to use OTC drugs as required until day 5. Each parent was allocated two identical bottles with either active and placebos drugs. Drugs were in liquid form. The dose for each was calculated based on the child's weight and the parent instructed how much to give. Parents asked to give drugs regularly (proactive) from 4 to 24 hours, and give further treatment from 24 to 48 hours based on the child's symptoms (reactive).	Investigators, research nurses and parents blinded to allocation. <u>**Setting**</u> 35 sites in Bristol, UK. 30 GP practices, 2 GP out-of-hours services, EM department at Children's hospital, one walk-in centre and NHS direct. Subjects recruited at site by nurse (locally), remotely (information faxed to research nurse) or community (parents directly contacted research nurse). <u>**Sample size calculation based on**</u>**:** 90% power detecting two sided alpha of 0.027 for detecting difference of time without fever of 30 minutes (SD 80 minutes) within first four hours and discomfort normal at 48 hours was 60% compared to 75% required total sample size of 747. Revised due to poor recruitment to 80% power and shorter SD of 50 minutes. Sample size of 180 would be sufficient. <u>**Outcome measures**</u> Temperature: measured using axillary temperature probe for first 24 hours then by parent at	No discomfort at 48 hours: 34, 37, 36 **Secondary outcomes** **Baseline** No discomfort: 3, 5, 5 Normal activity: 3, 4, 4 Normal appetite: 5, 3, 4 Normal sleep: 8, 3, 4 **Outcomes at 24 hours** Mean (SD) time to first fever clearance (minutes): 71.0 (69.1), 42.2 (33.5), 45.5 (34.3) Mean time (SD) without fever in first 24 hours (minutes): 940.3 (362.9), 1055.2 (329.7), 1217.4 (237.6) No discomfort: 22, 36, 29 Normal activity: 20, 20, 23 Normal appetite: 10, 14, 14 Normal sleep: 17, 13, 20 **Outcomes at 48 hours** Normal activity: 31, 37, 28	groups 3. Axillary temperature of 37.8C may not be considered as fever, as there is no agreed standard 4. Blinding may not have been complete due to parents being able to identify test drugs 5. Difficulties with recruitment meant that sample may not be generalisible. **Other information** <u>**Authors conclusions**</u> Ibuprofen should be first choice and consider the relative benefits and risks of using paracetamol and ibuprofen over 24 hours. <u>**Blinding**</u> Concern that blinding not complete as parents could guess if ibuprofen or paracetamol being given, but there was no evidence that

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Normal: 3, 5, 5 Not quite normal: 31, 27, 30 Some pain or distress:18, 18, 14 Crying or very distressed: 0, 2, 3 <u>Activity</u> Normal: 3, 4, 4 Quiet for longer than usual: 12, 18, 23 Hardly moving about:31, 19, 19 Not moving about willingly:6, 11, 6 <u>Appetite</u> Normal: 5, 3, 4 Eating less than normal: 12, 14, 10 Eating much less than normal: 35, 33, 36 Vomiting or refusing food or drink: 0, 2, 2 <u>Sleep</u>		48 hours and day 5 Symptom survey: discomfort, reduced activity, reduced appetite, and disturbed sleep measured at baseline, 24 hours, 48 hours and 5 days Adverse events: new or worsening symptoms **<u>Statistical methods</u>** Linear and logistic regression with Dunnett's and Tukey's adjustment for multiple comparisons.	Normal appetite: 21, 22, 21 Normal sleep: 27, 31, 25 **Outcomes at 5 days** No discomfort: 43, 38, 38 Normal activity: 44, 39, 37 Normal appetite: 29, 29, 32 Normal sleep: 31, 25, 27 **<u>Adverse events</u>** Diarrhoea: 10, 9, 12 Vomiting: 6, 3, 2 Rash: 2, 2, 1 Cough: 2, 0, 1 Cold to touch: 0, 3, 2 **<u>Drug use (by group)</u>** Paracetamol or placebo in 48 hours 1: 52, 52, 52	parent tried to guess allocation, with parental guesses being as expected by chance.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Normal: 8, 3, 4 More than usual: 20, 21, 20 More disturbed than usual: 9, 15, 10 A lot more disturbed than usual: 15, 13, 18 <u>Diagnosis</u> Otitis media: 7, 11, 8 Respiratory tract infection: 12, 15, 17 Non-specific viral illness: 21, 20, 16 Other: 12, 8, 11 **Inclusion criteria** Aged between 6 months and 6 years Unwell with a temperature between 37.8C to 41.0C Illness could be managed at home **Exclusion criteria** Required admission to hospital			2: 52, 49, 51 3: 50, 49, 49 4: 42, 39, 38 5: 35, 26, 24 6: 20, 11, 15 7: 8, 6, 6 8: 3, 1, 1 9: -, 1, - Ibuprofen or placebo in 48 hours 1: 52, 52, 52 2: 51, 49, 51 3: 45, 45, 46 4: 32, 34, 29 5: 18, 5, 18 6: 7, 4, 10 7: - , 1, 3	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Clinically dehydrated Recently participated in another trial Previously participated in the PITCH trial Contraindication to using test drugs Had any of the following: chronic neurological, cardiac, pulmonary (except asthma), liver or renal disease Parents unable to read or write English				
Full citation Pashapour,N., Macooei,A.A., Golmobammadlou,S., Alternating ibuprofen and acetaminophen in the treatment of febrile hospitalized children aged 9-24 months, Iranian Journal of Pediatrics, 19, 164-168, 2009 **Ref Id** 150014 **Country/ies where the study was carried out** Iran **Study type** Randomised control trial	**Sample size** 76 cases. 7 cases excluded as parents withdraw consent. **Characteristics** Variable: Acetaminophen (n = 35), acetaminophen and ibuprofen (n = 35) Age (mean months, SD): 17.0 (5.1), 17.2 (5.0), 0.8 Gender male: 19, 18, 0.7 Weight (kg): 11.9 (3.03), Fever: 39.3 (0.47), 39.2 (0.52)	**Interventions** **<u>Control group</u>** Acetaminophen 15 mg/kg every 4 hours **<u>Case group</u>** Ibuprofen 10mg/kg alternated with acetaminophen 15 mg/kg every 4 hours	**Details** **<u>Study design</u>** Written consent obtained Patients randomly separated into group. (Method of randomisation not mentioned) Sample size calculation - 20 subjects needed to find 30% difference in fever reduction between groups **<u>Setting</u>** Two tertiary paediatric units	**Results** **<u>Time, temperature in acetaminophen group, Temperature in alternating group</u>** Baseline: 39.3 (0.47), 39.2 (0.52), 0.03 2 hours: 38.8 (0.47), 38.8 (0.59), 0.7 4 hours: 38.5 (0.30), 38.4 (0.34), 0.048 5 hours: 38.2 (0.38), 38.0 (0.47), 0.04 7 hours: 38.2 (0.57), 38.0 (0.47), 0.04 8 hours: 38.0 (0.52), 37.7 (0.46), 0.02	**Limitations** Method of randomisation not described in detail Non-bacterial subjects only Unclear in which order drugs were given in alternating group Unclear how temperature was measured **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Compare the clinical effectiveness of acetaminophen alone with an alternative regimen of acetaminophen and ibuprofen in hospitalised infants aged 9 to 24 months with fever of non-bacterial origin. **Study dates** March 2006 to December 2007 **Source of funding** Not stated	0.03 **Inclusion criteria** Rectal temperature >= 38.5C Hospitalised Aged between 9 and 24 months **Exclusion criteria** Intolerance or major complications associated with administered drugs Clinical or laboratory evidence of bacterial infection. Based on stool analysis, stool culture, cell blood count, CRP, ESR, chest x-rays, electrolytes, blood sugar, blood urea nitrogen and creantinine. Did not complete study		**Outcome measures** Temperature at baseline, 2, 4, 5, 7, and 8 hours **Statistical methods** Univariate analysis using chi-square and t-tests	No major adverse events recorded Drop-out excluded from analysis. 35 subjects in each group.	**Author conclusion** Alternating acetaminophen and ibuprofen is more effective than acetaminophen alone at reducing fever in children aged 9 to 24 months.
Full citation Paul,I.M., Sturgis,S.A., Yang,C., Engle,L., Watts,H., Berlin,C.M.,Jr., Efficacy of standard doses of Ibuprofen alone, alternating, and combined with acetaminophen for the treatment of febrile children, Clinical Therapeutics, 32, 2433-2440, 2010 **Ref Id**	**Sample size** 60 children met inclusion criteria and were enrolled. All children completed the 6 hour observation period. Unclear how many children were accessed for inclusion. However, children seen more than once during study period. A total of 46 children	**Interventions** **Group A** Ibuprofen (10mg/kg) given at 0 hours **Group B** Ibuprofen	**Details** **Study design** Informed consent from parent obtained before entry Randomisation via computer generated log.	**Results** **Temperature of subjects in C, mean (SD)** **Time: ibuprofen alone (n = 20), ibuprofen + acetaminophen (n = 20), ibuprofen followed by acetaminophen (n = 20)**	**Limitations** Lack of blinding of subjects or research staff Use of temporal artery thermometry which can be unreliable compared to other measurements

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
150176 **Country/ies where the study was carried out** USA **Study type** Randmoised controlled trial **Aim of the study** Compare the antpyretic effect of 3 different treatment regimens in children, using either ibuprofen alone, ibuprofen combined with acetaminophen or ibuprofen followed by acetaminophen over a single 6 hour period. **Study dates** March 2006 to July 2009 **Source of funding** Grant from George L. Laverty Foundation and NIH grant. No industry involvement in study.	were recruited, 8 participated twice and 3 took part 3 times, and 35 took part once only. **Characteristics** **Variable: ibuprofen alone (n = 20), ibuprofen + acetaminophen (n = 20), ibuprofen followed by acetaminophen (n = 20)** Age (years), mean (SD): 3.2 (1.9), 3.0 (1.9), 4.0 (2.8) Sex (male): 12 (60%), 10 (50%), 7 (35%) Weight (kg), mean (SD): 15.3 (6.4), 13.6 (4.3), 16.8 (6.8) **Inclusion criteria** Temperature => 38C on temporal artery thermometer Subjects cooperative with temperature measurement and to taking medications **Exclusion criteria** Received acetaminophen within 6 hours Received ibuprofen, aspirin or other NSAIDs within 8 hours of presentation	(10mg/kg) + acetaminophen (15 mg/kg) given at 0 hours **Group C** Ibuprofen (10mg/kg) given at 0 hours then acetaminophen (15 mg/kg) given at 3 hours	Blinding not mentioned Sample size calculation was 120 subjects to achieve 80% power to detect 0.5C difference in temperature between groups at p = 0.05 **Setting** Children presenting at research centre or an onsite day-care center. **Statistical methods** Univariate analysis undertaken using Chi-squared, Fisher exact test and ANOVA to compare single time points. Also, mixed model used to assess change in measures of temperature over time. Bonferroni adjustment used to account for type 1 error inflation. **Outcomes** Temperature measured at baseline, 1, 2, 3, 4, 5 and 6 hours. Measured at least twice at each point until consecutive	Hour 0: 38.8 (0.9), 38.6 (0.4), 38.7 (0.9) Hour 1: 37.6 (0.5), 37.4 (0.5), 37.6 (0.4) Hour 2: 37.1 (0.4). 37.0 (0.5), 37.2 (0.3) Hour 3: 37.2 (0.6), 36.9 (0.4), 36.9 (0.4) Hour 4: 37.5 (1.1), 36.9 (0.3), 36.9 (0.3) Hour 5: 38.0 (1.1), 36.9 (0.5), 36.9 (0.3) Hour 6: 38.5 (1.5), 37.2 (0.6), 36.9 (0.3) **Number of subjects with temperature <38C** **Time: ibuprofen alone (n = 20), ibuprofen + acetaminophen (n = 20), ibuprofen followed by acetaminophen (n = 20)** Hour 0: 0, 0, 0 Hour 1: 16, 18, 16 Hour 2: 19. 20, 20 Hour 3: 18. 20, 20 Hour 4: 14. 20, 20 Hour 5: 12. 20, 20	Short study period meant that it was unlikely adverse events would emerge and did not examine long-term effect of treatment regimens **Other information** Children could participate more than once in the trial, but required a two week wash-out period. Limited to morning fever only to allow study protocol to be administered **Authors conclusions** Combined and alternating acetaminophen and ibuprofen provide greater antipyretic effect than ibuprofen alone at 4 and 6 hours.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Weight > 60kg (to avoid overdose prescription) History of adverse reactions to study medications Any of the following conditions: diabetes mellitus, renal dysfunctional, hepatic dysfunction, thromcocytopenia or dehydration apparent Severity of underlying illness precluded involvement.		measures were within 0.2C	Hour 6: 10. 19, 20 **Difference between groups using pairwise comparisons** **Time: ibuprofen alone vs. ibuprofen + acetaminophen, ibuprofen alone vs. ibuprofen followed by acetaminophen, ibuprofen + acetaminophen vs. ibuprofen followed by acetaminophen** Hour 0: 0.22 (0.22); 0.08 (0.22); -0.13 (0.22) Hour 1: 0.16 (0.18); -0.01 (0.18); -0.17 (0.18) Hour 2: 0.19 (0.18); 0.03 (0.18); -0.16 (0.18) Hour 3: 0.33 (0.19); 0.22 (0.19); -0.11 (0.19) Hour 4: 0.56 (0.18)*; 0.55 (0.18)*; -0.01 (0.18) Hour 5: 0.89 (0.18)*; 1.02 (0.18)*; 0.13 (0.18) Hour 6: 1.31 (0.22)*; 1.63 (0.22)*; 0.31 (0.22) * p<0.05	
Full citation Erlewyn-Lajeunesse,M.D.S.,	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Coppens,K., Hunt,L.P., Chinnick,P.J., Davies,P., Higginson,I.M., Benger,J.R., Randomised controlled trial of combined paracetamol and ibuprofen for fever, Archives of Disease in Childhood, 91, 414-416, 2006 **Ref Id** 150516 **Country/ies where the study was carried out** UK **Study type** Open labelled three arm RCT **Aim of the study** To assess the short term effectiveness of a combined dose of paracetamol and ibuprofen in reducing childhood fever. **Study dates** October 2004-January 2005 **Source of funding** Funded by the Anthony Hopkins Memorial Prize, awarded by the Faculty of Accident and Emergency Medicine as an unrestricted award to the Emergency Department.	n=123 **Characteristics** PARACETAMOL GROUP Median age in years (range): 1.5 (0.6-9.5) Median weight in kg (range): 11.4 (7.0-47.0) Sex (%): Not reported Diagnosis: Not reported Mean temperature at baseline (SD): 38.93 (0.68) IBUPROFEN GROUP Median age in years (range): 1.5 (0.5-9.6) Median weight in kg (range): 12.0 (7.5-33.0) Sex (%): Not reported Diagnosis: Not reported Mean temperature at baseline (SD): 38.73 (0.63) PARACETAMOL AND IBUPROFEN Median age in years (range): 2.4 (0.6-8.2) Median weight in kg (range):	PARACETAMOL GROUP n=41 Dose of paracetamol (SD): 15.3*mg/kg (2.0) *One child received a dose of 27.8mg/kg in error IBUPROFEN GROUP n=42 Dose of ibuprofen (SD): 5.0 mg/kg (0.2) PARACETAMOL AND IBUPROFEN n=40 Dose of paracetamol (SD): 14.9 (0.8) Dose of ibuprofen (SD): 4.9 (0.2)	Treatment regimen -Participants received suspensions of paracetamol 15mg/kg, ibuprofen 5mg/kg or both (no other details reported) Sample size calculation -A temperature difference of 1.0^{o}C at one hour was judged to be of clinical significance. To have an 80% chance of detecting this difference, at the two sided 5% level and including a 15% drop out rate before one hour, 40 children per group were required. Definition and measurement of fever - Fever was defined as >/=38^{o}C - Temperatures were measured normally by a single observer in the presenting ear using a tympanometric thermometer (Thermoscan, Braun Ltd, UK) at the time of admission, the time medication was given (TO), one hour later (T1) and 2 hours later (T2) if the child had not been discharged. Painful ears were avoided. - A temperature difference of 1^{o}C at 1 hour was defined as clinically significant Outcome measurement	Temperature at 1 hour (Mean +/-SD) Paracetamol group: 37.98 +/- 0.47 Ibuprofen group: 37.81 +/- 0.69 Paracetamol and ibuprofen: 37.59 +/- 0.61 Mean reduction of temperature at 1 hour (95%CI): Paracetamol group: 0.95 (0.72-1.17) Ibuprofen group: 0.92 (0.70-1.14) Paracetamol and ibuprofen: 1.22 (0.95-1.50) Pairwise comparisons-mean baseline adjusted difference at 1 hour: Paracetamol and ibuprofen vs. paracetamol alone: 0.35^{o}C; 95%CI: 0.10-0.60; p=0.028 Paracetamol and ibuprofen vs. ibuprofen alone: 0.25^{o}C; 95%CI: -0.01-0.50; p=0.166 Paracetamol vs. ibuprofen: 0.10^{o}C; 95%CI: -0.15-0.36; p=0.735 Adverse events: - The child who received a paracetamol dose of 27.8mg/kg in error did not suffer any adverse effects from this overdose. There were no other adverse effects.	- Indirect population as study included children aged between 6 months and 10 years - Though adverse effects from an overdose was not experienced, one child in the paracetamol group received a dose of 27.8mg/kg (instead of 15mg/kg) in error - The study was carried out in a paediatric emergency department and therefore only examined the short term control of pyrexia. A longer measurement period might produce different results, as the maximum decrease in temperature for both medicines is around 3 hours post-dose. **Other information** - Subjects were from inner city Children's Emergency Department

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	12.6 (7.9-25.0) Sex (%): Not reported Diagnosis: Not reported Mean temperature at baseline (SD): 38.81 (0.79) **Inclusion criteria** - Consecutive children between 6 months and 10 years attending the children's Emergency Department with fever of 38.0C or more **Exclusion criteria** - Children who had received paracetamol or ibuprofen in the previous six hours - Children with severe or life threatening infection - Children with suspected chicken pox - Children with cellulitis or other spreading skin infection - Children known to be immunosuppressed - Children allergic to either paracetamol or ibuprofen - Children medicated with warfarin, heparin, or antihypertensive		-Primary outcome measure was the child's temperature at one hour (i.e. change in temperature) -Secondary outcomes included temperature at 2 hours and time spent in the department -Only a small proportion of children had data at two hours to allow meaningful comparison, as they had already been discharged home -Secondary outcome analysis of the time spent on the unit did not add to findings and is not reported -No data on discomfort Intention to treat analysis -All children with data at one hour (n=108) were included in the primary analysis on an intention to treat basis (method not reported). Other information -Informed consent obtained -Allocation sequence was block randomised and generated independently of the research team		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Children with symptoms of active gastrointestinal bleeding - Children with known coagulopathy - Children with acute jaundice - Children likely to be suffering from dehydration, defined as more than four episodes of diarrhoea or vomiting in the previous 24 hours - Children with asthma, defined as a need for regular "preventer" medication - Children with chronic renal, liver or cardiac failure				
Full citation Figueras,Nadal C., Garcia de Miguel,M.J., Gomez,Campdera A., Pou,Fernandez J., Alvarez,Calatayud G., Sanchez,Bayle M., Paediatric Fever Co-operative Group from the Spanish Paediatric Association, Effectiveness and tolerability of ibuprofen-arginine versus paracetamol in children with fever of likely infectious origin, Acta Paediatrica,Acta Paediatr., 91, 383-390, 2002 **Ref Id** 151706 **Country/ies where the study was carried out**	**Sample size** n = 199 **Characteristics** Ibuprofen/L-arginine group: Mean age ± SD= 3.48±2.7 (0.5 to 11) years Mean body weight ±SD = 16.59±8.14 (4 to 45) kg Sex(male, female) n = 52 (52%), n = 48 (48%) Diagnosis: URTI = 41 (41.0%) Lower RTI = 12 (12.0%5) Gastrointestinal infections = 9 (9.0%) Upper UTI = 7 (7.0%) Soft tissue infection = 5	**Interventions** 1) Ibuprofen/L-arginigne (n = 100) single dose 6.67 ibuprofen mg/kg. 2) Paracetamol (n = 99) single dose 10.65mg/kg.	**Details** <u>Recruitment:</u> 199 patients were included in the study, 100 in the ibuprofen/L-arginigne and 99 in the paracetamol group. 12 children (6 in each group) were excluded because did not conform to study protocol. Efficacy and safety were therefore evaluated on 187 children following the intention to treat (ITT) analysis. 140 children did not reach the 8 hours but the data available before cessation were included in the ITT analysis. Ibuprofen/L-arginigne group n = 94	Results <u>Efficacy results:</u> Ibuprofen/L-arginigne group Mean temperature (°C) ± SD; time point. 39.14±0.60; Baseline 38.80±0.65; 20 min 38.24±0.72; 40 min 37.93±0.72; 60 min 37.61±0.73; 90 min 37.50±0.74; 2 h 37.57±0.92; 3 h 37.82±1.05; 4 h 37.88±1.07; 5 h 37.87±0.96; 6 h 38.00±1,33; 8 h. Paracetamol group	**Limitations** **Other information** 1) A minimum of 4h wash out was mandatory before inclusion for children who had revived antipyretic drugs within 4h of inclusion. Whenever possible a period of 6h wash out should have elapsed for those children who had been given a non-betactamic antibiotic 6h before initiation of the study.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Spain **Study type** Multicentre RCT. **Aim of the study** The aim of this study was to assess the paediatric antipyretic efficacy of a new ibuprofen formulation containing L-arginine for gastric protection, compared with the efficacy of paracetamol. **Study dates** From November 1998 to July 1999. **Source of funding** This study was supported by a grant from Zambon SA Pharmaceutical Company, Barcelona (Spain).	(5.0%) Otitis = 1 (1%) Other = 50(25.0%) Mean initial tympanic temperature ±SD = 39.14±0.60. Paracetamol group: Mean age ± SD= 3.78±3.0 (0.58 to 12) years Mean body weight ±SD = 18.56±11.32 (6.6 to 60) kg Sex (male, female) n = 60 (60.6%), n = 39 (39.4%) Diagnosis: URTI = 50 (50.5%) Lower RTI = 16 (16.1) Gastrointestinal infections = 3 (3.1%) Upper UTI = 3 (3.1%) Soft tissue infection = 7 (7.1%) Otitis = 0 Other = 20(20.2%) Mean initial tympanic temperature ±SD = 39.13±0.56. **Inclusion criteria** - Age (05 to 12 years) - Fever confirmation ≥0.5^{o}C the maximum normal range value of tympanic temperature according with age. - Body weight over the 3rd percentile. - Absence of CNG infection symptoms. - Absence of bilateral otitis or any other condition that the		Paracetamol group n = 93 Methods: This is a double-blind double-dummy multicentre study. Patients were randomly in 2 balanced groups to receive a single oral dose. Following randomisation, the study medication was administrated and the tympanic temperature was measured at 20 and 40 min, 1,5, 2, 3, 4, 5, 6 and 8 hours the clinical condition and vital signs at 2, 4, 6 and 8 hours. Adverse events were assessed and recorded thought the study. Intervention: The patients received either 1drop ibuprofen/L-arginine kg body weight (6.67 ibuprofen mg/kg) or 4 drops of paracetamol mol/kg (10.65mg/kg) together with matching placebo. Statistical analysis: the sample size required for the evaluation of the antipyretic efficacy was calculated on the basis of between-group comparison of the changes in tympanic temperature (C^{o}) registered 4h after treatment. The planned sample size amounted to a total of 170 evaluable patients, with 85 patients per treatment arm. Demographic and baseline characteristic were checked for homogeneity: quantitative	Mean temperature (°C) ± SD; time point. 39.13±0.60; Baseline 38.86±0.73; 20 min 38.32±0.75; 40 min 38.06±0.72; 60 min 37.78±0.70; 90 min 37.67±0.78; 2 h 37.78±0.92; 3 h 37.97±1.02; 4 h 37.85±0.87; 5 h 38.10±0.97; 6 h 38.20±0.84; 8 h. Antipyretic activity Mean change in T °C^{o} at 4 h ± SD = Ibuprofen/L-arginigne group 1.3±1.1; Paracetamol group 1.20±0.96; *p*-value = 0.52. Reduction of T °C at 4 h (%) ± SD = Ibuprofen/L-arginigne group 65.88±53.85; Paracetamol group 66.81±50.22; *p*-value = 0.96. Maximum T^{o}C change ± SD = Ibuprofen/L-arginigne group 1.91±0.96; Paracetamol group 1.76±0.89; *p*-value = 0.205. Mean time to become apyrexial (min) ± SD = Ibuprofen/L-arginigne group 75.1±5.17; Paracetamol group 77.02±5.81; *p*-value = 0.515. Children with a temperature reduction ≥ 1.5^{o}C (%) = Ibuprofen/L-arginigne group 33.2; Paracetamol group 28.6; *p*-value = 0.260.	2) 12 patients (6 in each group) were excluded because of vomiting with in 30min (11 cases) and spitting out the medication (1 case) following drug administration. Efficacy and safety were therefore evaluated on 187 patients, following the intention-to-treat analysis procedure. A total of 140 patients did not reach the 8h period (there was difference in the number of patients that did not reach the 8h period between the groups), the main reason for stopping was the need for a rescue medication and a subsequent improvement in the fever, with normalisation of the body temperature within 2 to 6 h of drug administration. Data available from these patients before cessation of the study were considered for the intention-to-treat analysis. 3) Adverse events and concomitant therapy were assessed and recorded throughout

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	investigators judged inadvisable to enrol the patient in the study. **Exclusion criteria** Children with a previous history of intestinal malabsorption. Children with febrile crisis over the past 6 months. Children with hypersensitivity to NSAIDs or paracetamol. Children with gastrointestinal bleeding. Children with significant renal, hepatic, neurological or CNS dysfunctions. Children with uncontrolled diabetes. Children with clotting alteration. Children with current diagnosis of diabetes. Children that had been treated with antibiotics within 24h of admission.		variables were analysed using X^2 test, and Student's *t*-test was used to for age, weight and laboratory results. Incident of adverse events were compared between treatments groups using χ^2 test.	<u>Children with a temperature reduction ≥ 2.5°C (%) =</u> Ibuprofen/L-arginigne group 22.11; Paracetamol group 15.58; *p*-value = 0.043. <u>Children with reduction of temperature to a normal range (%) =</u> Ibuprofen/L-arginigne group 43.22; Paracetamol group 40.70; *p*-value = 0.422. <u>Overall Efficacy</u> *p*-value = 0.363 <u>Recovery</u> Ibuprofen/L-arginigne group = 45.22 (42%); Paracetamol group = 40.86 (38%). <u>Improvement</u> Ibuprofen/L-arginigne group = 23.65 (22%); Paracetamol group = 24.73 (23%). <u>Unchanged</u> Ibuprofen/L-arginigne group = 16.12 (15%); Paracetamol group = 16.12 (15%). <u>Failure</u> Ibuprofen/L-arginigne group = 15.05 (14%); Paracetamol group = 18.28 (17%). <u>Tolerability results:</u> 19 (9.5%) children experienced in total adverse events.(mild to moderate no serious). <u>Overall Tolerability</u> *p*-value = 0.331 <u>Excellent</u> Ibuprofen/L-arginigne group = 60.2	the study. 4) Prohibited medication included: - other antipyretic drugs - non-betalactamic antibiotic - coumanin-like anticoagulants - antiepileptic drugs - analgesic and sedative or hypnotic drugs.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(59%); Paracetamol group = 65.6 (63%). Good Ibuprofen/L-arginigne group = 31.6 (31%); Paracetamol group = 30.2 (29%). Moderate Ibuprofen/L-arginigne group = 1.02 (1%); Paracetamol group = not reported. Poor Ibuprofen/L-arginigne group = 7.1 (7%); Paracetamol group = 4.2 (4%). Antipyretic activity Mean change in T^{o}C at 4 h ± SD = Ibuprofen/L-arginigne group 1.3±1.1; Paracetamol group 1.20±0.96; *p*-value = 0.52. Reduction of T^{o}C at 4 h (%) ± SD = Ibuprofen/L-arginigne group 65.88±53.85; Paracetamol group 66.81±50.22; *p*-value = 0.96. Maximum T^{o}C change ± SD = Ibuprofen/L-arginigne group 1.91±0.96; Paracetamol group 1.76±0.89; *p*-value = 0.205. Mean time to become apyrexial (min) ± SD = Ibuprofen/L-arginigne group 75.1±5.17; Paracetamol group 77.02±5.81; *p*-value = 0.515. Children with a temperature reduction ≥ 1.5^{o}C (%) = Ibuprofen/L-arginigne group 33.2; Paracetamol group 28.6; *p*-value = 0.260.	

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				Children with a temperature reduction ≥ 2.5°C (%) = Ibuprofen/L-arginigne group 22.11; Paracetamol group 15.58; *p*-value = 0.043. Children with reduction of temperature to a normal range (%) = Ibuprofen/L-arginigne group 43.22; Paracetamol group 40.70; *p*-value = 0.422. Overall Efficacy *p*-value = 0.363 Recovery Ibuprofen/L-arginigne group = 45.22 (42%); Paracetamol group = 40.86 (38%). Improvement Ibuprofen/L-arginigne group = 23.65 (22%); Paracetamol group = 24.73 (23%). Unchanged Ibuprofen/L-arginigne group = 16.12 (15%); Paracetamol group = 16.12 (15%). Failure Ibuprofen/L-arginigne group = 15.05 (14%); Paracetamol group = 18.28 (17%). Tolerability results: 19 (9.5%) children experienced in total adverse events.(mild to moderate no serious). Overall Tolerability p-value = 0.331	

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				Excellent Ibuprofen/L-arginigne group = 60.2 (59%); Paracetamol group = 65.6 (63%). Good Ibuprofen/L-arginigne group = 31.6 (31%); Paracetamol group = 30.2 (29%). Moderate Ibuprofen/L-arginigne group = 1.02 (1%); Paracetamol group = not reported. Poor Ibuprofen/L-arginigne group = 7.1 (7%); Paracetamol group = 4.2 (4%).	
Full citation Walson,P.D., Galletta,G., Chomilo,F., Braden,N.J., Sawyer,L.A., Scheinbaum,M.L., Comparison of multidose ibuprofen and acetaminophen therapy in febrile children, American Journal of Diseases of Children,Am.J.Dis.Child., 146, 626-632, 1992 **Ref Id** 151707 **Country/ies where the study was carried out** Columbus, Ohio, US. **Study type** RCT (double-blind, multidose, parallel-	**Sample size** n= 100. **Characteristics** <u>Ibuprofen group</u>: <u>2.5mg/kg (n = 15)</u> Mean age ± SD= 6.1±2.6 years Mean body weight ±SD = 21.7±11.1 kg Sex(male, female) n = 8, n = 7 Diagnosis: All children had infectious illness, in most cases viral pharyngitis. 5 children had a concurrent secondary diagnoses on study entry (1 had tinea, 1 accidental perineal trauma and 3allergic rhinitis). Mean baseline temperature	**Interventions** Treatment with either ibuprofen (2.5, 5.0, 10.0mg/kg) or acetaminophen (5.0mg/kg). Administration of antibiotics or intravenous fluids was allowed only after at least 24 hours of treatment with the assigned drug.	**Details** <u>Recruitment:</u> 64 children were enrolled in the study. 3 children were excluded because did not conform to study protocol. 61 children were included in the efficacy analysis. 45 in the ibuprofen group and 16 in the acetaminophen group. <u>Methods:</u> This is a double-blind double-dummy block-randomized, multi dose, parallel group study. Children were assigned to a treatment group and hospitalise for up to 48 hours and treated with either ibuprofen or acetaminophen every 6 hours. Oral or rectal temperature was measured hourly in the first 6 hours, every 3 hours for the	Results <u>Antipyretic efficacy</u> Fever reduction and length of treatment (Area under the curve (AUC) with respect to time) Mean % decrease in temperature <u>0 to 6 h</u> <u>Ibuprofen group (2.5mg/kg)</u> = 34.5%; AUC = 261* <u>Ibuprofen group (5mg/kg)</u> = 38.9%; AUC = 297 <u>Ibuprofen group (10mg/kg)</u> = 73.2%[§]; AUC = 385 <u>Acetaminophen group (15mg/kg)</u> = 65.9%; AUC = 377. Mean % decrease in temperature <u>0 to 12 h</u> <u>Ibuprofen group (2.5mg/kg)</u> = 73.1%;	**Limitations** ? **Other information** No differences were found between the four treatment groups in the demographic parameters or baseline temperature. No child in the study used antibiotics before 24 hours after the initial dose The children responses to treatment were evaluated before the researcher were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
group, variable-duration). **Aim of the study** To determine whether febrile children receiving 2.5-, 5-, or 10-mg/kg ibuprofen therapy via a liquid or 15-mg/kg acetaminophen therapy via an elixir every 6 hours for 24 to 48 hours show equivalent fever reduction or suffer adverse effects of the drug administered. **Study dates** Not reported. **Source of funding** Funded by Boots Pharmaceuticals Ltd, Sherveport, LA.	±SD = 39.4±0.4 °C 5.0 mg/kg (n = 15) Mean age ± SD= 5.8±2.8 years Mean body weight ±SD = 21.3±6.4 kg Sex(male, female) n = 6, n = 9 Diagnosis: All children had infectious illness, in most cases viral pharyngitis. 5 children had a concurrent secondary diagnoses on study entry (1 had tinea, 1 accidental perineal trauma and 3allergic rhinitis). Mean baseline temperature ±SD = 39.4±0.3 °C 10.0 mg/kg (n = 15) Mean age ± SD= 4.9±3.1 years Mean body weight ±SD = 20.1±11.3 kg Sex(male, female) n = 9, n = 6 Diagnosis: All children had infectious illness, in most cases viral pharyngitis. 5 children had a concurrent secondary diagnoses on study entry (1 had tinea, 1 accidental perineal trauma and 3allergic rhinitis). Mean baseline temperature ±SD = 39.4±0.4^{o}C Acetaminophen group: 15.0 mg/kg (n = 16) Mean age ± SD= 5.2±3.0 years Mean body weight ±SD =		next 30 hours and every 6 hours for the last 12 hours of the study. Intervention: The children received every 6 hours two liquids one containing the placebo one the active drug. Ibuprofen = 2.5, or, 5.0, or 10.0mg/kg Acetaminophen = 5.0mg/kg. Statistical analysis: The demographic data in the patient in the four treatment group were compared using c^2 test. All efficacy parameters were analysed with parametric ANOVA. Power calculation was not reported.	AUC = 696 Ibuprofen group (5mg/kg) = 58.2%; AUC = 689 Ibuprofen group (10mg/kg) = 84.0%[§]; AUC = 929 Acetaminophen group (15mg/kg) = 94.3%; AUC = 938. Mean % decrease in temperature 0 to 24 h Ibuprofen group (2.5mg/kg) = 79.6%; AUC = 1721 Ibuprofen group (5mg/kg) = 62.9%; AUC = 1572 Ibuprofen group (10mg/kg) = 67.8%[§]; AUC = 1995 Acetaminophen group (15mg/kg) = 87.5%; AUC = 2100 Mean % decrease in temperature 0 to 48h Ibuprofen group (2.5mg/kg) = 88.6%; AUC = 3810 Ibuprofen group (5mg/kg) = 70.5%; AUC = 3286 Ibuprofen group (10mg/kg) = 80.0%[§]; AUC = 3933 Acetaminophen group (15mg/kg) = 89.4%; AUC = 4400	informed to which children were assigned to each treatment group.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	20.8±10.7 kg Sex(male, female) n = 7, n = 9 Diagnosis: All children had infectious illness, in most cases viral pharyngitis. 5 children had a concurrent secondary diagnoses on study entry (1 had tinea, 1 accidental perineal trauma and 3allergic rhinitis). Mean baseline temperature ±SD = 39.3±0.3 °C. **Inclusion criteria** Children aged 6 months to 11 years 7 months, weighing 6.8 to 56.1 kg who had been febrile for less than 48 hours (febrile defined as oral or rectal temperature of 39 ^{o}C to 40.5 ^{o}C) but otherwise healthy children. Were included only children that had previously taken ibuprofen and/or acetaminophen without serious adverse effects. **Exclusion criteria** Children were excluded if they have taken any temperature-altering drug within 16 hours before the study or required antibiotic treatment from 12 hours before the initial dose of study medication to 24 hours after the first dose.				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Children with significant gastrointestinal, renal, hepatic, cardiac, haematologic, bronchospastic, malignant, or central nervous system diseases (including seizure disorders), vomiting, severe diarrhoea, dehydration, and children who had received investigational drugs within 1 month on the beginning of the study.				
Full citation Wong,A., Sibbald,A., Ferrero,F., Plager,M., Santolaya,M.E., Escobar,A.M., Campos,S., Barragan,S., De Leon,Gonzalez M., Kesselring,G.L., Fever Pediatric Study Group, Antipyretic effects of dipyrone versus ibuprofen versus acetaminophen in children: results of a multinational, randomized, modified double-blind study, Clinical Pediatrics,Clin.Pediatr., 40, 313-324, 2001 **Ref Id** 151709 **Country/ies where the study was carried out** Argentina, Chile, Brazil, Mexico **Study type** Multi centre CRT. **Aim of the study**	**Sample size** n= 628 **Characteristics** Ibuprofen group (n = 209): The dose was give based to initial temperature (T_o): T_o<39.2^oC = 5 mg/kg; T_o≥39.2^oC = 10 mg/kg; Mean age ± SD= 29±19 months (6 to 83 months); Mean body weight ±SD = 13±4 kg (6 to 28 kg); Sex(male, female) n = 118 (56%), n = 91 (44%); Tympanic T_o (^oC) ± SD = 39.2±0.6. Diagnosis: Upper RTI = 134 (64%); Lower RTI = 40 (19%); Gastrointestinal infections = 26 (12%); UTI = 10 (5%); Other = 39 (19%). Acetaminophen group (n =	**Interventions** Ibuprofen group (n = 209): The dose was give based to initial temperature (T_o): C<39.2^oC = 5 mg/kg; T_o≥39.2^oC = 10 mg/kg. Acetaminophen group (n = 210): Average dose bade on age 12 mg/kg. Dipyrone group (n = 209): Dose 15 mg/kg.	**Details** Recruitment: 628 children age between 6 months and 6 years of age were enrolled in the study and randomized to receive the study drugs (ibuprofen group n = 209, acetaminophen group n = 210 and dipyrone group n = 209) all these children were evaluated for the tolerability analysis . Children who remained in the study for at least 2 hours were included in the analysis. 555 children completed the study (ibuprofen group n = 185, acetaminophen group n = 191 and dipyrone group n = 179). And were evaluated for the efficacy analysis. Methods: This is a multiracial, multinational, multicentre, prospective, randomized, single oral dose, parallel group study. Tympanic temperature was measured	**Results** Antipyretic efficacy: Children (n) with tympanic temperature reduction ≥1.5^oC: Ibuprofen group (n = 185); n = 153 (83%). Acetaminophen group (n = 191); n = 148 (77%). Time to temperature reduction: Ibuprofen group (n = 185); Mean ±SD = 120±83; Range 15 to 360. Acetaminophen group (n = 191); Mean ±SD = 109±77; Range 15 to 360. Children (n) with normalised temperature (tympanic temperature ≤37.5^oC): Ibuprofen group (n = 185); n = 145 (78%). Acetaminophen group (n = 191); n = 130 (68%). Time to temperature normalisation: Ibuprofen group (n = 185);	**Limitations** **Other information** During the study anticonvulsant, antacids, corticosteroids, NSAIDs were not permitted. Also physical methods to lower the temperature were not permitted.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
This study compares the effect of acetaminophen, ibuprofen and dipyrone in children age 6 month to 6 years presenting with high fever. The secondary aim was to study the tolerability of these drugs. **Study dates** May to December 1998. **Source of funding** Not reported.	210): Average dose bade on age 12 mg/kg; Mean age ± SD= 31±21 months (6 to 91 months); Mean body weight ±SD = 13±5 kg (6 to 30 kg); Sex(male, female) n = 110 (52%), n = 100 (48%); Tympanic T_o (^oC) ± SD = 39.2±0.6. Diagnosis: Upper RTI = 145 (69%); Lower RTI = 44 (21%); Gastrointestinal infections = 25 (12%); UTI = 1 (0.5%); Other = 37 (18%). Dipyrone group (n = 209): Dose 15 mg/kg_ Mean age ± SD= 28±18 months (6 to 80 months); Mean body weight ±SD = 13±4 kg (6 to 26 kg); Sex(male, female) n = 128 (61%), n = 81 (39%); Tympanic T_o (^oC) ± SD = 39.3±0.6. Diagnosis: Upper RTI = 135 (64%); Lower RTI = 37 (18%); Gastrointestinal infections = 26(12%); UTI = 6 (3%); Other = 44 (21%). **Inclusion criteria** Children age between 6 months and 6 years of age, with body weight ≥5kg, able to		0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4,4 and 6 hours after the single dose of study medication. Intervention: 628 children were randomly assigned 1:1:1 to receive an oral single dose of: Ibuprofen group (n = 209): mean dose ± SD= 5.0±0.3 mg/kg and 9.7±1.1 mg/kg (according to T_o). Acetaminophen group (n = 210): mean dose ± SD= 11.8±0.3 mg/kg. Dipyrone group (n = 209): mean dose ± SD= 15.0±0.3 mg/kg. Statistical analysis: The total number of subjects (628) met the stipulated sample size of 180 patients per treatment arm, which was calculates on the hypothesis that the three treatment had a similar (null hypothesis) or different (alternative hypothesis) abilities to reduce the tympanic temperature 1.5^oC form baseline. This calculation assumed a statistical power of 0.90 and a statistical evaluated drop-out rate of 0.15.	Mean ±SD = 130±87; Range 15 to 360. Acetaminophen group (n = 191); Mean ±SD = 118±780; Range 15 to 360. Men change in tympanic temperature over time ±SD: Ibuprofen group (n = 185); 15 min = -0.21±0.49 [95%CI, -0.29; -0.14]; 30 min = -0.43±0.61 [95%CI, -0.52; -0.34]; 45 min = -0.75±0.65 [95%CI, -0.84; -0.64]; 60 min = -1.00±0.65 [95%CI, -1.10; -0.91]; 90 min = -1.33±0.66 [95%CI, -1.43; -1.24]; 2 hours = -1.56±0.72 [95%CI, -1.67; -1.46]; 3 hours = -1.58±0.81 [95%CI, -1.70; -1.47]; 4 hours = -1.44±0.98 [95%CI, -1.58; -1.29]; 5 hours = -1.35±1.06 [95%CI, -1.50; -1.20]; 6 hours = -1.24±1.08 [95%CI, -1.40; -1.09]. Acetaminophen group (n = 191); 15 min = -0.20±0.60 [95%CI, -0.29; -0.11]; 30 min = -0.44±0.61 [95%CI, -0.52; -0.35]; 45 min = -0.74±0.66 [95%CI, -0.83; -0.64]; 60 min = -1.15±0.70 [95%CI, -1.15; -0.96]; 90 min = -1.33±0.68 [95%CI, -1.43; -1.23];	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	receive oral medication, and presenting with tympanic temperature between 38.5^{o}C and 40.5^{o}C. The patients were identified ether form inpatient or from outpatient presenting to emergency clinic. **Exclusion criteria** Children with febrile seizures within the prior 6 months to the start of the study. Children with hypersensitivity to any of the study drugs. Children that had been treated with antipyretic drugs within 4 hours before the study onset. Children that had been treated with any of the investigational drugs within 4 weeks before the study onset. Children with poor prognosis 9tropical diseases, cramps, and /or severe dehydration). Children with connective tissues diseases. Children with AIDS. Children with haematological toxic effects within the past 3 months. Children that had been treated with antibiotic more than 12 hours before the study onset. Children with condition that might interfere with drug absorption.			2 hours = -1.55±0.68 [95%CI, -1.64; -1.45]; 3 hours = -1.52±0.79 [95%CI, -163; -1.40]; 4 hours = -1.47±0.91 [95%CI, -1.60; -1.34]; 5 hours = -1.34±1.05 [95%CI, -1.49; -1.19]; 6 hours = -1.20±1.09 [95%CI, -1.35; -1.04]. <u>Tolerability results:</u> <u>Total number of adverse events up to 14 days after study completion:</u> Ibuprofen group (n = 209); n = 22. Acetaminophen group (n = 210); n = 19. <u>Possible adverse events due to study medication:</u> Ibuprofen group (n = 209); n = 6 (27%). Acetaminophen group (n = 210); n = 3 (15%).	
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Autret,E., Breart,G., Jonville,A.P., Courcier,S., Lassale,C., Goehrs,J.M., Comparative efficacy and tolerance of ibuprofen syrup and acetaminophen syrup in children with pyrexia associated with infectious diseases and treated with antibiotics, European Journal of Clinical Pharmacology,Eur.J.Clin.Pharmacol., 46, 197-201, 1994
 	
Ref Id
 	
151710
 	
Country/ies where the study was carried out
 	
France
 	
Study type
 	
Multicentre RCT.
 	
Aim of the study
 	
The aim of the study was to evaluate the antipyretic action of ibuprofen in children younger than 5 years of age under the common condition prescription for one of an antipyretic i.e. in association with an antibiotic.
 	
Study dates
 	
The protocol was approved in October 1989.
 	
Source of funding
 	
Not reported.
	n= 154 children
	
	Characteristics
	
	Ibuprofen group:
	Mean age ± SD= 24.8±15.2 (6 to60) months
	Mean body weight ±SD = 11.8±3.1 kg
	Sex (male = n) = 47 (61%)
	Diagnosis:
	URTI = 78
	Bronchopulmonary infections = 20
	Other aetiology = 20
	Mean initial temperature ±SD = 39.02±0.72
	
	Acetaminophen group:
	Mean age ± SD= 22.9±15.1 (6 to60) months
	Mean body weight ±SD = 11.5±3.3 kg
	Sex (male = n) = 43 (55.8%)
	Diagnosis:
	URTI = 63
	Bronchopulmonary infections = 28
	Other aetiology = 21
	Mean initial temperature ±SD = 39.04±0.76
	
	Inclusion criteria
	
	Children age 6 months to 5 years, hospitalised for hyperthermia of infection origin. Requiring antipyretic and antibiotic treatment (either amoxicillin or amoxicillin-clavulanic acid).
		1) Ibuprofen plus an antibiotic (amoxicillin or amoxicillin-clavulanic acid) (n = 77).
		2) Acetaminophen plus an antibiotic (amoxicillin or amoxicillin-clavulanic acid) (n = 74).
			Recruitment:
			154 patients were enrolled in the study 77 in the ibuprofen and 77 in the acetaminophen group. 3 children were excluded because did not conform to study protocol. Therefore 151 children were included in the analysis of efficacy (77 in the ibuprofen and 74 in the acetaminophen group). 154 were included in the analysis of tolerability.
			All patients were followed up to 72h.
			Methods:
			this is a double-blind multicentre study. Patients were randomly assigned to one of the two parallel treatment groups. The rectal temperature was measured at the time of administration of the first dose and then 1, 2, 4, 6, 12, 24, 36, 48, 60 and 72 hours.
			Adverse events were assessed and recorded thought the study.
			Intervention:
			The patients were randomised to receive either ibuprofen (30mg/ml) syrup at a dose of 7.5mg/kg or acetaminophen (40mg/ml) syrup at a dose of 10mg/kg. The first dose was followed 6h later by a second dose administered regardless of the degree of hyperthermia. The following doses were given at regular intervals of 6h regular intervals if the temperature was above 37.8°C
				Antipyretic activity:
				Mean reduction of temperature at 4 h:
				Ibuprofen group = 60 (39%);
				Acetaminophen group = 45 (46%);
				p-value = 0.04;
				95%CI [0.01;0.29].
				Mean reduction of temperature between 0 and 4 h (°C):
				Ibuprofen group ± SD = 1.3±1;
				Acetaminophen group ± SD = 1.02±1.05;
				p-value = 0.07;
				95%CI [-0.03; 0.63].
				Mean time to become apyrexia (≤37.0°C) (min):
				Ibuprofen group ± SD = 513±28;
				Acetaminophen group ± SD = 580±33;
				p-value = 0.14.
				
				Sub group analysis;
				Children with initial temperature lower than 39°C:
				Ibuprofen group n = 37;
				Acetaminophen group n = 37.
				Area under the percent reduction temperature curve at 4 hours:
				Ibuprofen group± SD = 80.6±75.7;
				Acetaminophen group ± SD = 65±92.6;
				p-value = 0.43;
				95%CI [-22.9; 54.1].
				Area under the percent reduction temperature curve at 6 hours:
				Ibuprofen group ± SD = 134±126;
				Acetaminophen group ± SD = 116±152;
				p-value = 0.57;
				95%CI [-40.4; 83.2].
				Area under the percent reduction temperature curve at 12 hours:
				Ibuprofen group ± SD = 349±232;
				Acetaminophen group ± SD = 352±256;
				p-value = 0.96;
				95%CI [-116.6; 119.0].
					Other information
					
					1) 9 children (4 in the ibuprofen and 5 in the acetaminophen groups) did not follow the protocol, but they have been taken in account in the analysis accounting the principle of intention-to-treat.
					
					2) Patients might have had more than one manifestation of infection (see patient characteristics section)
					
					3) The children were no hospitalised. The study included 2 visits to a clinic one at the start of treatment one after 5 days. 95% of children (n = 332) were withdrawn from treatment before the second visit (5days) for similar reasons. A telephone interview was conducted 14 days after the inclusion to assess possible delayed adverse effects.
					
					4) Efficacy was assessed by the area under the percentage

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

	Base line temperature at least 38°C.
	
	Exclusion criteria
	
	Children that had ingested any antipyretic drugs up to 6 hours before the study. Children that had a history of hypersensitivity to non-steroidal anti-inflammatory drugs (including aspirin), to acetaminophen or to penicillin. Children with any conditions that might interfere with drug absorption or distribution, or severe hyperthermia with neurological and/or haemodynamic disorders. Children treated with anti-epileptic medications.
			up to a maximum of 30mg/kg in 24h for ibuprofen and 40mg/h for acetaminophen.
			Statistical analysis:
			the sample size (75 patients per group) was calculated to be able to detect a difference of 100%/h between area under the percentage reduction in temperature curves (AUC), or a fall in temperature of 30%, in the first 4 hours of drug administration (0h to 4h) with α = 0.05 and β = 0.1.
				Mean reduction of temperature at 4 h:
				Ibuprofen group = 0.52 (0.45%);
				Acetaminophen group = 0.46 (0.58%);
				p-value = 0.66;
				95%CI [-0.18;0.30].
				Mean reduction of temperature between 0 and 4 h (°C):
				Ibuprofen group ± SD = 0.77±0.76;
				Acetaminophen group ± SD = 0.80±0.96;
				p-value = 0.90;
				95%CI [-0.23; 0.57].
				
				Children with initial temperature equal or higher than 39°C:
				Ibuprofen group n = 40;
				Acetaminophen group n = 37.
				Area under the percent reduction temperature curve at 4 hours:
				Ibuprofen group ± SD = 113±54.5;
				Acetaminophen group ± SD= 89.1±49.5;
				p-value = 0.046;
				95%CI [0.77; 47.2].
				Area under the percent reduction temperature curve at 6 hours:
				Ibuprofen group ± SD= 183±87.5;
				Acetaminophen group ± SD = 134 ±90.6;
				p-value = 0.020;
				95%CI [8.7; 90.1].
				Area under the percent reduction temperature curve at 12 hours:
				Ibuprofen group ±SD = 440±166);
				Acetaminophen group ± SD = 347±169;
				p-value = 0.020;
				95%CI [17.2; 170.0].
				Mean reduction of temperature at 4 h =
				Ibuprofen group = 0.68 (0.31%);
				Acetaminophen group = 0.44 (0.40%);
				p-value = 0.003;
				95%CI [0.08;0.40].
				Mean reduction of temperature between
					in reduction curve compared to the initial temperature during the first 12 hours of treatment.
					
					5) Sub-group analysis of children less than 2 years of age and more than 2 years of age did not show any significant difference between treatments for any assessment criteria.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				0 and 4 h (^{o}C) = Ibuprofen group ± SD= 1.84±0.93; Acetaminophen group ± SD = 1.24±1.11; *p*-value = 0.010; 95%CI [0.13; 1.07].	
Full citation Ulukol,B., Koksal,Y., Cin,S., Assessment of the efficacy and safety of paracetamol, ibuprofen and nimesulide in children with upper respiratory tract infections, European Journal of Clinical Pharmacology, 55, 615-618, 1999 **Ref Id** 152343 **Country/ies where the study was carried out** Ankara, Turkey. **Study type** Open labelled RCT. **Aim of the study** The aim of this study was to assess and compare the efficacy and tolerability of paracetamol, ibuprofen and nimesulide in children with upper respiratory tract infections (URTIs). **Study dates** **Source of funding** Not specified	**Sample size** n = 90 **Characteristics** Ibuprofen group: Mean age ± SD= 4.7±2.5 (2 to 14) years Mean body weight ±SD = not reported Sex (male, female) n = 20, n = 10 Diagnosis: Viral URTIs n = 13 Streptococcal pharyngitis n = 9 Acute otitis media n = 8 Mean baseline axillary temperature ±SD = 38.71±0.43 ^{o}C. Paracetamol group: Mean age ± SD= 5.6±2.9 (2 to 14) years Mean body weight ±SD = not reported Sex (male, female) n = 15, n = 15 Diagnosis: Viral URTIs n = 13 Streptococcal pharyngitis n = 9 Acute otitis media n= 8 Mean baseline axillary	**Interventions** Paracetamol group: n = 30; dose10 mg/kg. Ibuprofen group: n = 30; dose10 mg/kg. Nimesulide group: n = 30; dose 2.5 mg/kg.	**Details** Recruitment: Ninety children with acute URTIs and fever were enrolled to the study. The patients were randomly assigned to a treatment group (n = 30 for each group). All children enrolled concluded the study. Methods: This is a randomised, open-labelled, parallel study Patients were randomly assigned to one of the three parallel treatment groups. The axillary temperature was measured at the time of administration of the first dose and then 1, 2, 3, and 4 hours. Adverse events were assessed and recorded thought the study on day 1. Afterwards, it was measured at least twice daily in the morning and evening for 5 days. Intensity of the symptoms, tolerance to the drugs and adverse events were assessed daily by using a rating scale(0 absent, 1 slight, 2 moderate, 3 severe). Intervention: The patients were allocated to three groups. The first group	**Results** Antipyretic activity: The mean difference in body temperature between baseline and the temperature at 4h for: Paracetamol ± SD= 1.29±0.71^{o}C: Ibuprofen ± SD= 1.86±0.74^{o}C. Data presented in graphical format, without standard deviations. Found significant difference between paracetamol and ibuprofen at 4-hours, but not at 1, 2, or 3 hours or day 1, 2, 3, 4 or 5. Symptoms relief efficacy results: Intensity of symptoms of the patients at entry and at 5 days of the treatment: Cough: On entry: Paracetamol n = 28; Ibuprofen n = 24. Decreased: Paracetamol n = 25; Ibuprofen n = 17. Unchanged/increased: Paracetamol n = 3: Ibuprofen n = 7. Rihnorrhoea: On entry: Paracetamol n = 20: Ibuprofen n = 22. Decreased:	**Limitations** Age range 2 to 14 years. **Other information** 1) The mean body temperature versus time was reported in graphs.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	temperature ±SD = 38.63±0.42 ^{o}C. Nimesulide group: Mean age ± SD= 5.7±3.7 (2 to 14) years Mean body weight ±SD = not reported Sex (male, female) n = 15, n = 15 Diagnosis: Viral URTIs n = 15 Streptococcal pharyngitis n = 3 Acute otitis media n = 11 Acute sinusitis n = 1 Mean baseline axillary temperature ±SD = 38.79±0.55^{o}C. **Inclusion criteria** Children age 2 to 14 years with acute febrile URTIs characterised from the following signs: axillary temperature greater than 38^{o}C; pharyngeal hyperaemia and pain; cough; nasal obstruction rihnorrhoea; adenopathy; anorexia and in impaired state of general health. **Exclusion criteria** The presence of a major infection (e.g. septicaemia, pneumonia, meningitis, requiring intravenous antibiotic treatment; the		was treated with paracetamol 10 mg/kg thrice daily; the second group with ibuprofen 10 mg/kg thrice daily; and the third group received nimesulide 2.5 mg/kg twice daily for 5 days. Statistical analysis: The demographic data in the patient in the four treatment group were compared using X^2 test. X^2 test was also used to compare the number of patients showing normal body temperature and alteration of symptoms density over the time of treatment between groups. Power calculation was not reported.	Paracetamol n = 16: Ibuprofen n = 19. Unchanged/increased: Paracetamol n = 4: Ibuprofen n = 3. Anorexia: On entry: Paracetamol n = 25: Ibuprofen n = 25. Decreased: Paracetamol n = 17: Ibuprofen n = 10. Unchanged/increased: Paracetamol n = 8: Ibuprofen n = 15 .	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	presence of haematological; renal and gastrointestinal diseases; hypersensitivity to any of the study drugs; used other drugs treatment during the 7 days before the entry to the study.				
Full citation Autret,E., Reboul-Marty,J., Henry-Launois,B., Laborde,C., Courcier,S., Goehrs,J.M., Languillat,G., Launois,R., Evaluation of ibuprofen versus aspirin and paracetamol on efficacy and comfort in children with fever, European Journal of Clinical Pharmacology, 51, 367-371, 1997 **Ref Id** 152347 **Country/ies where the study was carried out** France **Study type** Multicentre RCT. **Aim of the study** Compared efficacy and impact on the comfort of ibuprofen aspirin and paracetamol on children with fever aged 6 to 24 months. **Study dates** Not reported.	**Sample size** n= 348 children **Characteristics** Ibuprofen group: Mean age = not reported Mean body weight = not reported Sex = not reported Diagnosis = not reported Mean initial rectal temperature ±SD = 39.4±0.4 Paracetamol group: Mean age = not reported Mean body weight = not reported Sex = not reported Diagnosis = not reported Mean initial temperature ±SD = 39.3±0.4 Aspirin group: Mean age = not reported Mean body weight = not reported Sex = not reported Diagnosis = not reported Mean initial temperature ±SD = 39.3±0.4	**Interventions** 1) Ibuprofen (n = 116) dose of 7.5mg/kg. 2) Paracetamol (n = 116) dose of 10mg/kg. 3) Aspirin (n = 116) dose of 10mg/kg.	**Details** Recruitment: 351 patients were enrolled in the study 117 in the ibuprofen, 177 in the paracetamol and 117 in the aspirin group. 3 children were excluded because did not conform to study protocol. Therefore 348 children were included in the efficacy analysis (116 in the ibuprofen and 116 in the paracetamol group). Methods: This is a multicentre study open trial. The rectal temperature was measured before the administration of the first dose and then 1, 4, and 6 hours. The impact of treatment on the child's comfort was evaluated at 4 and 6 hour using general behaviour rating scales and of the relief after treatment. The parents' comfort was measured by their level of anxiety and by quality of their sleep. Intervention: The following three antipyretic drugs were compared: ibuprofen (20mg/ml) syrup at a dose	**Results** Mean reduction of temperature at 1 h (^{o}C) = Ibuprofen group n = 114; Paracetamol group n = 114; Ibuprofen group± SD= -0.97± 0.58; Paracetamol group = -0.90± 0.56; *p*-value = NS. Mean reduction of temperature at 4 h (^{o}C) = Ibuprofen group n = 112; Paracetamol group n = 110; Ibuprofen group± SD= -1.42± 0.85; Paracetamol group = -1.04± 0.85. Mean reduction of temperature at 6 h (^{o}C) = Ibuprofen group n = 108; Paracetamol group n = 108; Ibuprofen group± SD= -1.19± 0.94; Paracetamol group = -0.88± 0.85. Number of children with rectal temperature equal or lower than 38^{o}C (%):At 1 h; Ibuprofen group = 33 (29); Paracetamol group = 25 (22). At 4 h; Ibuprofen group = 69 (62); Paracetamol group = 45 (41). At 6h; Ibuprofen group = 43 (49);	**Limitations** **Other information** 1) 8 children (1 in the ibuprofen, 2 in the paracetamol and 5 in the aspirin group) were include by mistake (5 because the temperature was less than 39^{o}C and 3 because they were less than 6 months old or more than 24 months old) but they were taken in account in the intention-to-treat analysis. 35 children (12 in the ibuprofen, 10 in the paracetamol and 13 in the aspirin group) did not follow the protocol because they also received other antipyretic or an NSAID on day 1 but they were taken in account in the intention-to-treat analysis. 2) The antipyretic activity was assessed

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported.	**Inclusion criteria** Children 6 to 24 months old followed on an outpatient basis. Rectal temperature of at least 39^{o}C. **Exclusion criteria** Children were excluded if they had one of the following criteria: treatment by an antipyretic drugs up to 4 hours before the study inclusion; hypersensitivity to non-steroidal anti-inflammatory drugs (including aspirin), or paracetamol; any treatment or conditions that might interfere with drug absorption or distribution; or severe hyperthermia with neurological and/or haemodynamic disorders.		of 7.5mg/kg, paracetamol (30mg/ml) syrup at a dose of 10mg/kg and aspirin in sachets containing 150g at a dose of 10mg/kg. The first dose of antipyretic was given before 16:00h to facilitate follow-up by parents during the first 6h. No further dose was allowed in the 6h following the first, but subsequent doses were permitted if necessary. The maximum dose was of 30mg/kg in 24h for ibuprofen and was fixed by the paediatrician for paracetamol and aspirin. No other antipyretic drugs were allowed but antibiotics were permitted. <u>Statistical analysis:</u> The sample size (100 patients per group) was calculated on the basis of difference of 50% of the area under the curve (AUC) of the reduction in temperature with time and alpha risk of 5% and beta risk of 10%.	Paracetamol group = 40 (37). <u>Tolerability results:</u> <u>Number of children experiencing adverse events n (%)</u>: <u>Ibuprofen group</u> Gastrointestinal n = 4 (46%); Vomiting n = 2; Diarrhoea n = 4; Skin n = 3 (23%); Rush n = 3; Perinatal erythema n = -; Other n = 4 (31%); Hypoglycaemia n = 1; Agitation n = 3Total n = 13. <u>Paracetamol group</u> Gastrointestinal n = -; Vomiting n = - Diarrhoea n = - Skin n = - Rush n = - Perinatal erythema n = 1; Other n = - Hypoglycaemia n = - Agitation n = - Total n = 1.	by the area under the curve of percentage reduction in temperature with time.

Full citation
 	
Van,Esch A., Van Steensel-Moll,H.A., Steyerberg,E.W., Offringa,M., Habbema,J.D., rksen-Lubsen,G., Antipyretic efficacy of ibuprofen and acetaminophen in children with febrile seizures, Archives of Pediatrics and Adolescent Medicine, 149, 632-637, 1995
 	
Ref Id
	Sample size
	
	n = 72
	
	Characteristics
	
	Ibuprofen group:
	Mean age ± SD= 25.0±10.8 months
	Mean body weight ±SD = 13.2±2.8kg
	Sex (male%, female %) = 71%; 29%
		Interventions
		
		Ibuprofen n= 34; dose 5mg.kg.
		
		Acetaminophen n = 36; dose 10mg/kg.
			Details
			
			<u>Recruitment:</u>
			72 children age 10 months to 4 years were enrolled, 2 children were excluded because did not conform to study protocol. Therefore 70 children were included in the efficacy analysis (34n the ibuprofen and 36 in the acetaminophen group).
			<u>Methods:</u>
				Results
				
				<u>Antipyretic activity:</u>
				Ibuprofen group:
				<u>Time = 0h</u>
				n recording n(%) = 34(100);
				Mean (SEM) temperature ^{o}C = 39.12(0.14);
				n below 38.5^{o}C n(%) = 8(24).
				<u>Time = 2h</u>
				n recording n(%) = 30(88);
				Mean (SEM) temperature ^{o}C = 37.60(0.11);
					Limitations
					
					The population is children with a history of febrile seizures.
					
					Other information
					
					1) A crossover analysis comparing the study drugs was performed on 22 children with a second

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

152348
 	
Country/ies where the study was carried out
 	
Netherland
 	
Study type
 	
RCT.
 	
Aim of the study
 	
To compare the antipyretic efficacy of ibuprofen syrup (5 mg/kg per dose) and acetaminophen syrup (10 mg/kg per dose) in children with a history of febrile seizures.
 	
Study dates
 	
1st June 1992 to 1st October 1993.
 	
Source of funding
 	
Booth Pharmaceutical, Hilversum, Netherlands, and the Sophia Foundation for the Sick Child, Rotterdam, Netherlands.
	Diagnosis:
	Simple URTIs= 44%
	Extended URTIs = 24%
	Other = 32%
	Mean initial rectal temperature ±SD = 39.12±0.83°C.
	
	Acetaminophen group:
	Mean age ± SD= 24.7±9.5 months
	Mean body weight ±SD = 12.6±2.2kg
	Sex (male%, female %) = 53%; 47%
	Diagnosis:
	Simple URTIs= 33%
	Extended URTIs = 42%
	Other = 25%
	Mean initial rectal temperature ±SD = 39.23±0.79°C.
	
	Inclusion criteria
	
	Children who developed a rectal temperature at home of 38.5°C. Older than 10 moths and had no contraindication for ibuprofen and acetaminophen use.
	
	Exclusion criteria
	
	Children that used antipyretic or antibiotics drugs treatment during the 12 hours before the entry to the study.
			This is a randomized, multiple-dose, double-blind, and cross-over trial. Study medication (ibuprofen or acetaminophen) was given every 6 hours for 1 to 3 days. Rectal temperatures were recorded at 0, 2, 4, 6, 12, and 24 hours after the first dose.
			Adverse events were defined as new (or changes in) clinically important symptoms, sensitivity reaction, or injury during the study whether or not related to the treatment.
			Intervention:
			Ether Ibuprofen syrup (5mg.kg) or acetaminophen (10mg/kg). The medication was given for 1 to 3 days according with the duration of the fibril illness.
			Statistical analysis:
			Differences between the treatments groups in the performance of the respective measurements were analysed with Pearson's X^2 test. Temperature differences between patients' treatment with ibuprofen and acetaminophen were analysed by two-sample *t* test and analysis of covariance.
			Power calculation was not reported.
				n below 38.5°C n(%) = 27(90).
				Time = 4h
				n recording n(%) = 31(91);
				Mean (SEM) temperature °C = 37.38(0.18);
				n below 38.5°C n(%) = 26(84).
				Time = 6h
				n recording n(%) = 34(100);
				Mean (SEM) temperature °C = 37.82(0.22);
				n below 38.5°C n(%) = 20(59).
				Time = 12h
				n recording n(%) = 32(94);
				Mean (SEM) temperature °C = 37.87(0.24);
				n below 38.5°C n(%) = 21(66).
				Time = 24h
				n recording n(%) = 27(79);
				Mean (SEM) temperature °C = 37.92(0.22);
				n below 38.5°C n(%) = 20(74).
				
				Acetaminophen group:
				Time = 0h
				n recording n(%) = 36(100);
				Mean (SEM) temperature °C = 39.23(0.13);
				n below 38.5°C n(%) = 4(11).
				Time = 2h
				n recording n(%) = 29(81);
				Mean (SEM) temperature °C = 37.96 (0.17);
				n below 38.5°C n(%) = 22(76).
				Time = 4h
				n recording n(%) = 31(86);
				Mean (SEM) temperature °C = 37.95(0.23);
				n below 38.5°C n(%) = 22(71).
				Time = 6h
				n recording n(%) = 35(97);
				Mean (SEM) temperature °C = 38.23(0.22);
				n below 38.5°C n(%) = 18(51).
					episode of fever.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

				Time = 12h
				n recording n (%) = 35(97);
				Mean (SEM) temperature ^{o}C = 37.88(0.19);
				n below 38.5^{o}C n(%) = 24(69).
				Time = 24h
				n recording n(%) = 33(92);
				Mean (SEM) temperature ^{o}C = 38.18(0.22);
				n below 38.5^{o}C n(%) = 20(61).	

Full citation Sidler,J., Frey,B., Baerlocher,K., A double-blind comparison of ibuprofen and paracetamol in juvenile pyrexia, British Journal of Clinical Practice, Supplement. 70, 22-25, 1990 **Ref Id** 152355 **Country/ies where the study was carried out** Switzerland. **Study type** Multi centre RCT. **Aim of the study** This study was aimed to extend investigations with ibuprofen in children admitted urgently to hospital. To compare its efficacy of ibuprofen with paracetamol and to investigate the incident and severity of side effects. **Study dates**	**Sample size** n = 90 **Characteristics** Mean age ± SD= Not reported Mean body weight ±SD = Not reported Sex (male%, female %) = Not reported Diagnosis: Not reported Mean initial rectal temperature ±SD = Not reported. **Inclusion criteria** Children of either sex with age between 5 months and 13years, weighting between 7 and 36kg and having a rectal temperature of 38.5^{o}C or more. **Exclusion criteria** Children were excluded if they had one of the following	**Interventions** Ibuprofen n= 30; dose 7mg.kg; Ibuprofen n= 29; dose 10mg.kg; Paracetamol n = 30; dose10mg/kg.	**Details** Recruitment: 90 children were randomly allocated in one of the treatment group by random distribution in blocs such that the same number of children were initially for each group .One child was excluded from the efficiency analysis and the number of children for each study arm was: Ibuprofen 7mg.kg n= 30; Ibuprofen 10mg.kg n= 29; Paracetamol 10mg/kg n = 30. Methods: This is a randomized, multiple-dose, double-blind, and parallel group study. the children received the first dose at time 0h, a second and third dose of the study medication could be administrated only at 8h intervals, and only in case the rectal temperature was 38.3^{o}C or more. Rectal temperatures were recorded at 0, 0.25, 0.5, 1, 2, 3, 6, 8, 12, 16, 20 and 24 hours after the first dose. Intervention:	**Results** Antipyretic activity: Mean reduction of temperature at 3 h (^{o}C) = Ibuprofen group 7mg.kg = -1.64 ^{o}C; Ibuprofen group 10mg.kg = -2.09 ^{o}C Paracetamol group = -1.29 ^{o}C; *p value* (paracetamol/ibuprofen group 7mg.kg) = ≤0.05; *p value* (paracetamol/ibuprofen group 10mg.kg) = ≤0.01. Tolerability results: Number of children experiencing adverse events n = Ibuprofen group 7mg.kgm n = 3; Ibuprofen group 10mg.kg n = 1; Paracetamol group n = 2.	**Limitations** Included children older the 5 years. Children withdrawing from the study not included in calculation? **Other information** 89 children were eligible for the study 18 withdrew from the study. Ibuprofen group 7mg.kgm n = 3; Ibuprofen group 10mg.kg n = 4; Paracetamol group n = 11.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported. **Source of funding** Not reported.	criteria: • Severe systemic diseases including a bleeding disorder, a history of peptic ulceration, chronic dyspepsia or chronic gastrointestinal bleeding, or a history of asthma. • Children receiving: immunosuppressive treatment, or treatment that can interact with the study medications, treatment by antipyretic drugs up to 4 hours before the study inclusion. • Children having hypersensitivity to the study medications. • Children suffering from hepatic, renal or cardiac diseases. • Children unable to tolerate rectal probe. • Children considered unsuitable to enter the study by the study investigators.		Ibuprofen syrup 7mg.kg, syrup 10mg/kg or paracetamol syrup 10mg/kg. Statistical analysis: Power calculation was not reported.		
Full citation Walson,P.D., Ibuprofen versus paracetamol for the treatment of fever in children, British Journal of Clinical	**Sample size** n = 120 **Characteristics**	**Interventions** Ibuprofen group: n = 60; Mean dose ± SD=	**Details** Recruitment: 120 children were randomly allocated in one of the treatment group according to a	**Results** Antipyretic activity: Rectal temperature after treatment:	**Limitations** **Other information** 1) The temperature (^{o}C) versus the time

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Practice, Supplement. 70, 19-21, 1990 **Ref Id** 152356 **Country/ies where the study was carried out** France **Study type** RCT **Aim of the study** The aim of the study was to ascertain that the time if occurrence of the maximum antipyretic effect of a single dose of ibuprofen did not differ by more than 1 hour from that of paracetamol when both the drugs were given in the Sparkelets formulation to children with fever related to a bacterial or viral infection. **Study dates** October 1992 to December 1993 **Source of funding** Not reported.	<u>Ibuprofen group:</u> Mean age ± SD= 4.0±2.6: *p*-value = not significant Mean body weight ±SD = 16.1±5.2: *p*-value = not significant Sex (male n; female n) = 30; 30; *p*-value = not significant Diagnosis: Not reported Mean initial rectal temperature ±SD = 38.95±0.25^{o}C: *p*-value = not significant. <u>Paracetamol group:</u> Mean age ± SD= 4.2±2.5; *p*-value = not significant Mean body weight ±SD = 17.0±5.7: *p*-value = not significant Sex (male n; female n) = 29; 27: *p*-value = not significant Diagnosis: Not reported Mean initial rectal temperature ±SD = 38.94±0.27^{o}C: *p*-value = not significant. **Inclusion criteria** Children presenting to a private practitioner clinic with fever related to a bacterial or viral infection (treated at the clinic or at home) and the condition did not required initiation of an antibiotic treatment within less than 3 hours. Weight ≥10≥29kg, age approximately 2 to 10 years with a rectal temperature	10.3±1.9mg/kg. <u>Paracetamol group:</u> n = 56; Mean dose ± SD= 9.8±1.9mg/kg.	computer-generated randomization list 4 children were excluded because did not conform to study protocol. Therefore 116 children were included in the efficacy analysis (60 the ibuprofen and 56 in the paracetamol group). <u>Methods:</u> This is a randomized, single-dose, double-blind, multicentre (15 centres) equivalence trial. The children received the first dose at time 0h. Rectal temperatures were recorded at 0, 1, 2, 3, 4, and 6 hours after the first dose. A second dose of paracetamol (7.5 to mg/kg) was allowed as a rescue treatment is the child's temperature was higher than 39.5^{o}C, or if the temperature had not decreased by more than 0.5^{o}C at 4 hours from the first dose. <u>Intervention:</u> Ibuprofen Sparkelets formulation mean dose ± SD= 10.3±1.9mg/kg. Paracetamol Sparkelets formulation mean dose ± SD= 9.8±1.9mg/kg. <u>Statistical analysis:</u> The sample size was determined in a blind analysis, taking in to account an expected minimum T_{Max} difference of 1 hours between the two treatment groups and a residual variance of the main criteria in the first 20 children how interfered the study. Final analysis was performed	<u>0h</u> Ibuprofen group n = 60; Temperature (^{o}C) ± SD = 39.0±0.3; Paracetamol group n = 56; Temperature (^{o}C) ± SD = 38.9±0.3; *p*-value = not significant. <u>1h</u> Ibuprofen group n = 60; Temperature (^{o}C) ± SD = 38.4±0.6; Paracetamol group n = 56; Temperature (^{o}C) ± SD = 38.3±0.6; *p*-value = not significant. <u>2h</u> Ibuprofen group n = 58; Temperature (^{o}C) ± SD = 37.9±0.7; Paracetamol group n = 55; Temperature (^{o}C) ± SD = 37.9±0.7; *p*-value = not significant. <u>3h</u> Ibuprofen group n = 55; Temperature (^{o}C) ± SD = 39.0±0.3; Paracetamol group n = 56; Temperature (^{o}C) ± SD = 38.9±0.3; *p*-value = not significant. <u>4h</u> Ibuprofen group n = 58; Temperature (^{o}C) ± SD = 37.6±0.8; Paracetamol group n = 55; Temperature (^{o}C) ± SD = 37.8±0.8 *p*-value = not significant. <u>6h</u> Ibuprofen group n = 56; Temperature (^{o}C) ± SD = 38.0±0.8; Paracetamol group n = 55; Temperature (^{o}C) ± SD = 38.0±0.8; *p*-value = not significant. <u>Evaluation of the treatments under study within 6 hours after treatment:</u> Ibuprofen group n = 58; Paracetamol group n = 56; Ibuprofen group T_{max} (h) ± SD = 3.61±1.34;	after dosing (h) was plotted. 2) T_{Max} (h) is defined as when the lower temperature is observed between 0 and 6 hours. 3) Extent of temperature decrease (^{o}C) (dθ) is defined as the difference between the initial temperature and the T_{Max}.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	≥38.5≥39.5^{o} C. **Exclusion criteria** Personal history of febrile convulsion. Children with hypersensitivity to aspirin, NSAIDs, anti-inflammatory drugs or paracetamol. Children with known renal or hepatic insufficiency Children with history of gastrointestinal ulcer or vomiting making oral administration impossible. Children receiving a bath at 37^{o}C or administration of a cold pack within 1 hour before inclusion. Children that had been treated with aspirin, NSAIDs, anti-inflammatory drugs or paracetamol within 4hours before inclusion. Children that had been treated with antibiotics, anti-inflammatory drugs, corticosteroids within 8 hours before inclusion. Children using any anticoagulant treatment.		on an intention-to-treat basis. The compatibly of the treatment group was tested with χ^2 test. The 95%CI were calculated with Student's methods.	Paracetamol T_{max} (h) ± SD = 3.65±1.47; *p*-value = not significant, (95% CI –0.48; 0.56). Extent of temperature decrease (^{o}C) (dθ): Ibuprofen group dθ (^{o}C) ± SD = 1.65±0.80; Paracetamol dθ (^{o}C) ± SD = 1.50±061; *p*-value = not significant, (95% CI –0.41; 0.11). Rare of temperature decrease (^{o}C/h) (dθ ÷ T_{max}): Ibuprofen group dθ ÷ T_{max} (^{o}C/h) ± SD = 0.52±0.32; Paracetamol dθ ÷ T_{max} (^{o}C/h) ± SD = 0.51±0.38; *p*-value = not significant, (95% CI –0.45; 0.55). Ibuprofen group n=n 53 Duration of temperature below 38.5^{o}C (h) ± SD = 3.79±1.33; Paracetamol group n = 48 Duration of temperature below 38.5^{o}C (h) ± SD = 3.84±1.22; *p*-value = not significant, (95% CI –0.14; 0.12). Number of children whose temperature fell below 38.5^{o}C: Ibuprofen group n = 56; Paracetamol group n = 53.	
Full citation Brewer,E.J.,Jr., A comparative evaluation of indomethacin, acetaminophen and placebo as antipyretic agents in children, Arthritis and Rheumatism, 11, 645-651, 1968	**Sample size** 72 in acetaminophen 75 in placebo group **Characteristics**	**Interventions** Acetaminophen - 3mgm/ib Placebo	**Details** Ethic approval and informed consent not mentioned	**Results** **<u>Difference in mean temperature</u>** (°F) Acetaminophen reduced temperature significantly more than placebo at all times between 0.5 and 3 hours.	**Limitations** - Standard deviations not presented so data could not be reanalysed. - Acetaminophen and placebo treatments

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 152363 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** Comparison of indomethacin, acetaminophen and placebo **Study dates** Not stated **Source of funding** Grant from United States Public Health Service	Average age - acetaminophen = 2.75 vs. 2.74 for placebo Reason for treatment - URTI = 19 vs. 29 -LRTI = 15 vs. 13 - Measles = 16 vs. 19 - Gastric = 14 vs. 8 - Infection = 3 vs. 4 - Renal tract infection = 2 vs. 1 - Other = 3 vs. 0 **Inclusion criteria** Children aged under 14 Rectal temperature of 101 or more **Exclusion criteria** Not stated		**Setting** No stated **Methodology** Randomised Statistical methods not described	0.5 = 0.472 vs. 0.023 1 = 1.183 vs. 0.174 1.5 = 1.847 vs. -.240 2 = 2.248 vs. 0.348 2.5 = 2.603 vs. 0.457 3 = 2.600 vs. 0.483 **Adverse events** Acetaminophen = 1 vs. placebo = 0	looked different. - Some children treated for viral illnesses **Other information**
Full citation Vauzelle-Kervroedan,F., d'Athis,P., Pariente-Khayat,A., Debregeas,S., Olive,G., Pons,G., Equivalent antipyretic activity of ibuprofen and paracetamol in febrile children, Journal of Pediatrics,	**Sample size** n = 120 **Characteristics**	**Interventions** Ibuprofen group: n = 60; Mean dose ± SD=	**Details** Recruitment: 120 children were randomly allocated in one of the treatment group according to a	**Results** Antipyretic activity: Rectal temperature after treatment:	**Limitations** **Other information** 1) The temperature (^{o}C) versus the time

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
131, 683-687, 1997 **Ref Id** 152366 **Country/ies where the study was carried out** France **Study type** RCT **Aim of the study** The aim of the study was to ascertain that the time if occurrence of the maximum antipyretic effect of a single dose of ibuprofen did not differ by more than 1 hour from that of paracetamol when both the drugs were given in the Sparkelets formulation to children with fever related to a bacterial or viral infection. **Study dates** October 1992 to December 1993 **Source of funding** Not reported	<u>Ibuprofen group:</u> Mean age ± SD= 4.0±2.6: *p*-value = not significant Mean body weight ±SD = 16.1±5.2: *p*-value = not significant Sex (male n; female n) = 30; 30; *p*-value = not significant Diagnosis: Not reported Mean initial rectal temperature ±SD = 38.95±0.25^{o}C: *p*-value = not significant. <u>Paracetamol group:</u> Mean age ± SD= 4.2±2.5; *p*-value = not significant Mean body weight ±SD = 17.0±5.7: *p*-value = not significant Sex (male n; female n) = 29; 27: *p*-value = not significant Diagnosis: Not reported Mean initial rectal temperature ±SD = 38.94±0.27^{o}C: *p*-value = not significant. **Inclusion criteria** Children presenting to a private practitioner clinic with fever related to a bacterial or viral infection (treated at the clinic or at home) and the condition did not required initiation of an antibiotic treatment within less than 3 hours.	10.3±1.9mg/kg. <u>Paracetamol group:</u> n = 56; Mean dose ± SD= 9.8±1.9mg/kg.	computer-generated randomization list 4 children were excluded because did not conform to study protocol. Therefore 116 children were included in the efficacy analysis (60 the ibuprofen and 56 in the paracetamol group). <u>Methods:</u> This is a randomized, single-dose, double-blind, multicentre (15 centres) equivalence trial. The children received the first dose at time 0h. Rectal temperatures were recorded at 0, 1, 2, 3, 4, and 6 hours after the first dose. A second dose of paracetamol (7.5 to mg/kg) was allowed as a rescue treatment is the child's temperature was higher than 39.5^{o}C, or if the temperature had not decreased by more than 0.5^{o}C at 4 hours from the first dose. <u>Intervention:</u> Ibuprofen Sparkelets formulation mean dose ± SD= 10.3±1.9mg/kg. Paracetamol Sparkelets formulation mean dose ± SD= 9.8±1.9mg/kg. <u>Statistical analysis:</u> The sample size was determined in a blind analysis, taking in to account an expected minimum T_{Max} difference of 1 hours between the two treatment groups and a residual variance of the main criteria in the first 20 children how interfered the study.	<u>0h</u> Ibuprofen group n = 60; Temperature (^{o}C) ± SD = 39.0±0.3; Paracetamol group n = 56; Temperature (^{o}C) ± SD = 38.9±0.3; *p*-value = not significant. <u>1h</u> Ibuprofen group n = 60; Temperature (^{o}C) ± SD = 38.4±0.6; Paracetamol group n = 56; Temperature (^{o}C) ± SD = 38.3±0.6; *p*-value = not significant. <u>2h</u> Ibuprofen group n = 58; Temperature (^{o}C) ± SD = 37.9±0.7; Paracetamol group n = 55; Temperature (^{o}C) ± SD = 37.9±0.7; *p*-value = not significant. <u>3h</u> Ibuprofen group n = 55; Temperature (^{o}C) ± SD = 39.0±0.3; Paracetamol group n = 56; Temperature (^{o}C) ± SD = 38.9±0.3; *p*-value = not significant. <u>4h</u> Ibuprofen group n = 58; Temperature (^{o}C) ± SD = 37.6±0.8; Paracetamol group n = 55; Temperature (^{o}C) ± SD = 37.8±0.8 *p*-value = not significant. <u>6h</u> Ibuprofen group n = 56; Temperature (^{o}C) ± SD = 38.0±0.8; Paracetamol group n = 55; Temperature (^{o}C) ± SD = 38.0±0.8; *P-value* = not significant. <u>Evaluation of the treatments under</u>	after dosing (h) was plotted. 2) T_{Max} (h) is defined as when the lower temperature is observed between 0 and 6 hours. 3) Extent of temperature decrease (^{o}C) (dθ) is defined as the difference between the initial temperature and the T_{Max}.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Weight ≥10≥29kg, age approximately 2 to 10 years with a rectal temperature ≥38.5≥39.5^{o} C. **Exclusion criteria** Personal history of febrile convulsion. Children with hypersensitivity to aspirin, NSAIDs, anti-inflammatory drugs or paracetamol. Children with known renal or hepatic insufficiency Children with history of gastrointestinal ulcer or vomiting making oral administration impossible. Children receiving a bath at 37^{o}C or administration of a cold pack within 1 hour before inclusion. Children that had been treated with aspirin, NSAIDs, anti-inflammatory drugs or paracetamol within 4hours before inclusion. Children that had been treated with antibiotics, anti-inflammatory drugs, corticosteroids within 8 hours before inclusion. Children using any anticoagulant treatment.		Final analysis was performed on an intention-to-treat basis. The compatibly of the treatment group was tested with c^2 test. The 95%CI were calculated with Student's methods.	<u>study within 6 hours after treatment:</u> Ibuprofen group n = 58; Paracetamol group n = 56; Ibuprofen group T_{max} (h) ± SD = 3.61±1.34; Paracetamol T_{max} (h) ± SD = 3.65±1.47; *p*-value = not significant, (95% CI –0.48; 0.56). Extent of temperature decrease (^{o}C) (dθ): Ibuprofen group dθ (^{o}C) ± SD = 1.65±0.80; Paracetamol dθ (^{o}C) ± SD = 1.50±061; *p*-value = not significant, (95% CI –0.41; 0.11). Rare of temperature decrease (^{o}C/h) (dθ ÷ T_{max}): Ibuprofen group dθ ÷ T_{max} (^{o}C/h) ± SD = 0.52±0.32; Paracetamol dθ ÷ T_{max} (^{o}C/h) ± SD = 0.51±0.38; *p*-value = not significant, (95% CI –0.45; 0.55). Ibuprofen group n=n 53 Duration of temperature below 38.5^{o}C (h) ± SD = 3.79±1.33; Paracetamol group n = 48 Duration of temperature below 38.5^{o}C (h) ± SD = 3.84±1.22; *p*-value = not significant, (95% CI –0.14; 0.12). Number of children whose temperature fell below 38.5^{o}C: Ibuprofen group n = 56; Paracetamol	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				group n = 53.	

Full citation
 	
McIntyre,J., Hull,D., Comparing efficacy and tolerability of ibuprofen and paracetamol in fever, Archives of Disease in Childhood, 74, 164-167, 1996
 	
Ref Id
 	
152367
 	
Country/ies where the study was carried out
 	
UK
 	
Study type
 	
RCT
 	
Aim of the study
 	
The aim of this study was to compare antipyretic activity and tolerability of ibuprofen and paracetamol suspension in the treatment of febrile illness in children.
 	
Study dates
 	
Not reported.
 	
Source of funding
 	
Not reported.
	Sample size
	
	n = 150
	
	Characteristics
	
	<u>Ibuprofen group:</u>
	Median age = 1.8 years (range 0.4 to 11 years)
	Media body weight = 11.9 kg (range 6.7 to 45 kg)
	Sex (male n; female n) = 42; 34;
	Diagnosis: Not reported
	Mean initial axillary temperature = not reported.
	
	<u>Paracetamol group:</u>
	Median age = 1.6 years (range 0.2 to 9.4 years)
	Media body weight = 11.9 kg (range 5.8 to 34 kg)
	Sex (male n; female n) = 47; 27;
	Diagnosis:
	Febrile convulsion n = 35
	Mean initial axillary temperature = not reported.
	
	Inclusion criteria
	
	Children were inpatient of a single hospital, between 2 months and 12 years of age, of either sex and with axillary temperature of 37.5^{o}C or above.
		Interventions
		
		<u>Ibuprofen group:</u>
		n = 76;
		dose = 20mg/kg/24 hours.
		<u>Paracetamol group:</u>
		n = 74;
		dose = 50mg/kg/24 hours.
			Details
			
			<u>Recruitment:</u>
			150 children were randomly allocated in one of the treatment group. Randomization was in blocks of four to allow for equal number in each treatment group. All 150 children provided at least one valid post-baseline efficacy assessment and all these data were included in the analysis based on the internet to treat.
			<u>Methods:</u>
			This is a double-blind, parallel group, randomized, multiple dose study. The children received the first dose at time 0h. Axillary temperatures were recorded at 0, 1, 2, 3, 4, and 6 hours after the first dose or immediately before any subsequent dose.
			After the first dose palatability was recorded (determined according with age) using the following scale: from 0 = dislike to 4 like.
			Irritability was determined using the following scale: from 0 = very irritable to 2 not irritable.
			The change in clinical condition was determined using the following scale: from 0 = much worst to 2 much improved.
			After last study medication or when the fever had resolved,
				Results
				
				<u>Antipyretic activity:</u>
				<u>Mean change in baseline temperature at 4 h (^{o}C) =</u>
				Ibuprofen group = -1.8^{o}C;
				Paracetamol group = -1.6^{o}C;
				p-value = 0.39.
				
				<u>Number of children with temperature reduction ≥1^{o}C at 4hours:</u>
				Ibuprofen group n = 52/69 (75%);
				Paracetamol group n = 48/66 (73%);
				p-value = 0.73.
				
				<u>Median palatability score:</u>
				Ibuprofen group 2 (no reaction);
				Paracetamol group 2 (no reaction); *p*-value = 0.43.
				
				<u>Number of children with improved irritability score:</u>
				Ibuprofen group n = 9/50 (18%);
				Paracetamol group n = 21/56 (38%);
				p-value = 0.47.
				
				<u>Median score for change in clinical condition:</u>
				Ibuprofen group 3 (improved);
				Paracetamol group 3 (improved); *p*-value = 0.08.
				
				<u>Median score for overall efficacy:</u>
				Ibuprofen group 2 (good effect);
				Paracetamol group 2 (good effect); *p*-value = 0.16.
				
				<u>Tolerability results:</u>
				Number of children experiencing adverse events n (%)=
					Limitations
					
					Children age range.
					
					Mean initial axillary temperature was not reported.
					
					After 36hours only a small proportion of children remind in the study so the mean decreased in temperature after this time was not reported.
					
					Other information
					
					The change in temperature over the time was reported in a plot were the mean temperature was plotted vs. time of assessment.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Children with body weight below the third centile for their age. Children using any anticoagulant treatment Children with hypersensitivity to aspirin, NSAIDs, anti-inflammatory drugs or paracetamol. Children with history of gastrointestinal ulcer or bleeding. Children with known hart renal or hepatic sever insufficiency. Children with systemic disease including malignancy. Medication that might interfere with the study medication was not permitted during the study or within 6 hours before inclusion.		the overall efficacy of the medication was recorded using the following scale: from 0 = no effect to 3 very good effect. <u>Intervention:</u> Ibuprofen dose = 20mg/kg/24 hours. Paracetamol dose = 50mg/kg/24 hours. The study medication was administered orally six hourly if required, up to 4 doses in 24 hours, for a maximum of three days. <u>Statistical analysis:</u> The planned sample sized was 75 children per arm: with 90%power and 5%significance level, assuming a variability of 1.07^{o}C. The number of children experiencing adverse events and the number of those the temperature fell by 1^{o}C or more at the 4 hours were compared using the X^2 test.	Ibuprofen group n = 10/76 (13%); Paracetamol group n = 14/74 (19%); *p*-value = 0.34.	
Full citation Kauffman,R.E., Sawyer,L.A., Scheinbaum,M.L., Antipyretic efficacy of ibuprofen vs. acetaminophen, American Journal of Diseases of Children, 146, 622-625, 1992 **Ref Id** 152368 **Country/ies where the study was carried out** USA	**Sample size** n= 38 **Characteristics** Ibuprofen 7.5 mg/kg group: Mean age ± SD= 5.6±2.7 year Mean body weight ±SD = not reported Sex (female/male) = 8/4 Baseline temperature ±SD = 38.9±0.3 Ibuprofen 10 mg/kg group:	**Interventions** Each child was randomly assigned to receive a single dose of : Ibuprofen 7.5 mg/kg group n= 12 Ibuprofen 10 mg/kg group n= 8 Acetaminophen group n = 8 Placebo group n = 9	**Details** <u>Recruitment:</u> 38 patients were enrolled in the study in the study, 1 child was excluded because did not conform to study protocol. Therefore 37 children were included in the analysis. <u>Methods:</u> this is a double-dummy, double-blind, randomized, placebo-controlled trial. Patients were randomly assigned to receive a single oral dose. The temperature was measured before the	**Results** <u>Antipyretic response</u> Area under the curve (AUC) for percentage change in temperature from baseline over time: Ibuprofen 7.5 mg/kg group n = 12 Median AUC (≥95% CI) = 730 (576-839). Ibuprofen 10 mg/kg group n = 8 Median AUC (≥95% CI) = 590 (160-875). Acetaminophen 10 mg/kg group n = 9 Median AUC (≥95% CI) = 328 (-356-686). *P-value* compare with ibuprofen therapy = 0.05	**Limitations** **Other information** 1) Oral temperature was measured before dosing, 30 minutes after dosing, and hourly thereafter for 8 hours after the dose. 2) Patients were monitored for adverse effects during the study and 24 hours after administration of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT. **Aim of the study** To compare the antipyretic efficacy of ibuprofen, placebo, and acetaminophen. **Study dates** **Source of funding** This study was partially supported by a grant from Boots Pharmaceutical Inc, Shreveport, La.	Mean age ± SD= 6.8.±2.8 year Mean body weight ±SD = not reported Sex (female/male) = 2/6 Baseline temperature ±SD = 38.9±0.3 Acetaminophen group: Mean age ± SD= 5.3±3.4 year Mean body weight ±SD = not reported Sex (female/male) = 7/1 Baseline temperature ±SD = 39.0±0.6 Placebo group: Mean age ± SD= 5.8.±2.7 year Mean body weight ±SD = not reported Sex (female/male) = 6/3 Baseline temperature ±SD = 38.9±0.4 Diagnoses were as follows: fever without apparent focus of infection n = 8 herpetic stomatitis n = 1 otitis media n = 7 acute pharyngitis n=n 10 pneumonia n = 3 acute sinusitis n = 1 viral URTI n = 7 **Inclusion criteria** Patient were required to have an oral temperature oral temperature of 38.3^{o}C or		study medication was taken, then 30 min, 1, 2, 3, 4, 5, 6 an8 8 hours after dosing. Intervention: 12 children received a single dose of ibuprofen 7.5 mg/kg. 8 children received a single dose of ibuprofen 10 mg/kg. 8 children received a single dose of acetaminophen. Statistical analysis: Statistical analysis and power calculation were not reported.	Placebo n = 9 Median AUC (≥95% CI) = 3-67 (-629-120). *p*-value compare with active treatments = <0.01	the assigned drug. 3) Temperature failure was defined as either a temperature increase of 0.55^{o}C above the baseline temperature or an absolute temperature grater then 40^{o}C at any time during the 8h observation period. 4) A plot of mean temperature over time was reported, showing no significant difference between the ibuprofen treatments was detected at any time. The mean temperatures in the ibuprofen groups were significant lower than the placebo group between 1 and 6 hours. The mean temperatures in the acetaminophen group were significant lower than the placebo group between 3 and 5 hours. The mean temperatures were lower in the group receiving ibuprofen 7.5 mg/kg than the acetaminophen group between 3 and 5 hours.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	higher for at least 1 h before enrolment. **Exclusion criteria** Ingestion of an antipyretic medication within 8h before starting the study. Administration of an antibiotic before enrolment. Administration of intravenous fluids during the study. Hypersensitivity to aspirin and other non-steroidal anti-inflammatory drugs. History of gastrointestinal conditions. Renal, hepatic, cardiac, malignant or hematopoietic disease. Asthma, diabetes, dehydration or seizures associated with the present illness.				

Full citation
 	
Wilson,J.T., Brown,R.D., Kearns,G.L., Eichler,V.F., Johnson,V.A., Bertrand,K.M., Lowe,B.A., Single-dose, placebo-controlled comparative study of ibuprofen and acetaminophen antipyresis in children, Journal of Pediatrics, 119, 803-811, 1991
 	
Ref Id
 	
152369
 	
Country/ies where the study was carried out
	Sample size
	
	n = 178
	
	Characteristics
	
	Mean age ± SD= 3.36±0.22 years
	Mean body weight ± SD= 15.1±0.56 kg
	Sex (male n; female n) = not reported
	Diagnosis: not reported
	Mean T_i range = 39.1 to 39.2^{o}C.
		Interventions
		
		<u>Ibuprofen group:</u>
		dose = 5mg/kg;
		<u>Ibuprofen group:</u>
		dose = 10mg/kg;
		<u>Paracetamol group:</u>
		dose = 12.5mg/kg;
		<u>Placebo.</u>
			Details
			
			<u>Recruitment:</u>
			178 children were randomly allocated in one of the treatment group on the basis of their age an initial rectal temperature . All 178 children's data were included in the analysis.
			<u>Methods:</u>
			This is a dose ranging and placebo controlled, single dose, modified double-blind approach study. Rectal temperature was recorded 15 min before the study medication was administrated.
				Results
				
				<u>Antipyretic activity:</u>
				<u>Maximum antipyresis after a dose of each treatment:</u>
				<u>Acetaminophen n= 52:</u>
				Time ± SD= 3.72±0.20 hours;
				T_i ± SD= 37.53±0.12^{o}C;
				ΔT_n at maximal effect ± SD= 0.53±0.12^{o}C;
				ΔT_i at maximal effect ± SD= -1.58±0.12^{o}C;
				%Eff at maximal effect ± SD= 76.80±6.29.
				
				<u>Ibuprofen (5mg/kg) n = 43:</u>
				Time ± SD= 3.81±0.23 hours;
					Limitations
					
					The demographic profile or the study groups was not specific.
					
					Age range outside the scope.
					
					Other information
					
					AUC: are under the curve;
					ΔT: change in temperature;

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
USA **Study type** RCT and retrospective analysis of previously collected data. **Aim of the study** Ibuprofen was evaluated as an antipyretic agent in 178 children (age 3 months to 12 years)to compare dosage (dose 5 vs. 10 mg/kg), establish absolute efficacy (with placebo control group), determine relative efficacy (ibuprofen vs. acetaminophen) , evaluate maximum efficacy and identify potential confounding variable. **Study dates** Not reported. **Source of funding** Not reported.	**Inclusion criteria** Children age 3 months to 12 years identified in either the outpatient paediatric clinic or the inpatient ward, with rectal temperature of at least 38.3^{o}C but not exceeding 40.5^{o}C **Exclusion criteria** Children with history of febrile seizure within 6 months. Children that had been treated with investigation drugs up to 4 weeks before inclusion. Children that had been treated with antibiotics up to 12 hours before inclusion. Children that had been treated with antipyretics within 2 hours before inclusion. Children with hypersensitivity to aspirin, NSAIDs, anti-inflammatory drugs or paracetamol. Children with malignant diseases. Depending on the judgement of the investigators children were excluded if they had severe medical illness, condition that interfere with drugs absorption, history of haematological toxic effects within 3 months of the start of the study.		Subsequently the temperatures were recorded at 0.5, 1, 1.5, 2, 3, 4, 5 and 6 hours after dosing; when possible they were also recorded at 7, 8, 10 and 12 hours. <u>Intervention:</u> Ibuprofen dose = 5mg/kg; Ibuprofen dose = 10mg/kg; Paracetamol dose = 12.5mg/kg; Placebo dose = 0.5ml/kg. <u>Statistical analysis:</u> Several temperature measurements were subject to an area under the curve analysis. The level of significance accepted for all the test was a = 0.05. Power calculation was not reported.	T_i ± SD= 37.52±0.12^{o}C; ΔT_n at maximal effect ± SD= 0.52±0.12^{o}C; ΔT_i at maximal effect ± SD= -1.68±0.12^{o}C; %Eff at maximal effect ± SD= 78.812±4.80. <u>Ibuprofen (10mg/kg) n = 47:</u> Time ± SD= 3.95±0.18 hours; T_i ± SD= 37.20±0.20^{o}C; ΔT_n at maximal effect ± SD= 0.20±0.12^{o}C; ΔT_i at maximal effect ± SD= -1.79±0.13^{o}C; %Eff at maximal effect ± SD= 92.28±6.91. <u>Placebo n = 22:</u> Time ± SD= 4.25±0.33 hours; T_i ± SD= 38.77±0.23^{o}C; ΔT_n at maximal effect ± SD= 1.77±0.23^{o}C; ΔT_i at maximal effect ± SD= -0.35±0.23^{o}C; %Eff at maximal effect ± SD= 14.88±11.88. <u>Area under the curves AUCs (0 to 6 hours) related to the antipyretic effect after a dose of each treatment:</u> <u>Acetaminophen n= 51:</u> AUC of T_i ± SD= 229.53±0.40; AUC of ΔT_n at time t ± SD= 6.72±0.58; AUC of ΔT_i at time t ± SD= -5.93±0.51; AUC of %Eff ± SD= 284.48±24.15. <u>Ibuprofen (5mg/kg) n = 43:</u> AUC of T_i ± SD= 229.69±0.40; AUC of ΔT_n at time t ± SD= 7.09±0.58; AUC of ΔT_i at time t ± SD= -6.15±0.54;	ΔT_i: change in temperature from initial temperature; ΔT_n: change in temperature required to reduce to normal temperature; %Eff: percentage of efficacy; $\%Eff_t$: percentage of efficacy at a given time; T_i: initial temperature; T_t: temperature at a given time. ΔT_i at a time was plotted versus time.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				AUC of %Eff ± SD= 281.83±22.07. <u>Ibuprofen (5mg/kg) n = 47:</u> AUC of T_i ± SD= 228.21±0.33; AUC of ΔT_n at time t ± SD= 4.91±0.47; AUC of ΔT_i at time t ± SD= -7.06±0.52; AUC of %Eff ± SD= 357.91±23.97. <u>Placebo n = 22:</u> AUC of T_i ± SD= 232.82±0.58; AUC of ΔT_n at time t ± SD= 11.70±0.83; AUC of ΔT_i at time t ± SD= -1.03±0.67; AUC of %Eff ± SD= 41.96±33.74. <u>AUCs (0 to 6 hours) of ΔT_n at time t, as effected by T_i:</u> <u>T_i <38.83°C:</u> <u>Acetaminophen n= 19:</u> mean ± SD= 4.19±0.69°C.. <u>Ibuprofen (5mg/kg) n = 15:</u> mean ± SD= 4.63±0.66°C. <u>Ibuprofen (10mg/kg) n = 21:</u> mean ± SD= 3.16±0.64°C. <u>Placebo n = 9:</u> mean ± SD= 9.80±1.04°C. <u>T_i ≥38.83°C:</u> <u>Acetaminophen n= 32:</u> mean ± SD= 8.22±0.72°C.. <u>Ibuprofen (5mg/kg) n = 28:</u> mean ± SD= 8.42±0.70°C. <u>Ibuprofen (10mg/kg) n = 26:</u> mean ± SD= 6.31±0.56°C. <u>Placebo n = 13:</u> mean ± SD= 13.01±0.42°C.	
Full citation Walson,P.D., Galletta,G., Braden,N.J., Alexander,L., Ibuprofen, acetaminophen, and placebo treatment of febrile children, Clinical Pharmacology and	**Sample size** n = 127 **Characteristics**	**Interventions** <u>Ibuprofen group:</u> dose = 5mg/kg; n = 29. <u>Ibuprofen group:</u>	**Details** <u>Recruitment:</u> 127children were randomly allocated in one of the four treatment group on the basis of	**Results** <u>Antipyretic activity:</u> Hourly mean temperature <u>Ibuprofen (5mg/kg) n = 29:</u> 0h; mean T ± SD= 102.3±0.7°F	**Limitations** The population was divided by starting temperature not type

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Therapeutics, 46, 9-17, 1989 **Ref Id** 152371 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** Compared the efficacy tolerability, safety and dose response of 5mg/kg and 10 mg/kg ibuprofen suspension, 10mg/kg A elixir and placebo liquid in children (2 to 11 year) with fever (101 to 104°F; 38.84 to 40°C). **Study dates** Not reported. **Source of funding** Not reported.	<u>Patient stratification by temperature</u> **:** High Temperature 102.6 to 104.0°F (39.46 to 40°C) No antibiotic n= 49; Antibiotic n= 3. Low Temperature 101.0 to 102.5°F (38.84 to 39.42°C) No antibiotic n= 63; Antibiotic n= 3. <u>All subjects n = 118</u> Age range = 2 to 11years Mean age = 5.8 years Median age = 6.0 years Weight range = 10.8 to 73.0 kg Mean body weight = 22.7 kg Media body weight = 20.4 kg Sex (male n; %) = 55 (46.6%) Diagnosis not reported Mean baseline oral temperature = 102.4°F (39.38°C) antibiotic treatment: No antibiotic n = 112 antibiotics n = 6. <u>Low temperature group</u> Age range = 2 to 11years Mean age = 6.1 years Median age = 6.0 years Weight range = 11.9 to 73.0 kg Mean body weight = 23.7 kg Media body weight = 20.4 kg Sex (male n; %) = 34 (51.5%) Diagnosis not reported Mean baseline oral temperature = 101.8°F	dose = 10mg/kg; n = 25. <u>Acetaminophen group:</u> dose = 10mg/kg; n = 31 <u>Placebo group:</u> n = 33.	their initial oral temperature and exposure to antibiotics . All 118 were included in the analysis. <u>Methods:</u> This is a single-oral-dose and placebo controlled, double-blind , triple-dummy study. Oral temperature was recorded 0 hour, before the study medication was administrated. Subsequently the temperatures were recorded at 0.5, 1, 2, 3, 4, 5, 6 and 8 hours after dosing. <u>Intervention:</u> Ibuprofen dose = 5mg/kg; Ibuprofen dose = 10mg/kg; Paracetamol dose = 10mg/kg; Placebo liquid. <u>Statistical analysis:</u> Tests for treatment differences in the efficacy parameters, maximum percent reduction and area under the percent reduction time curve through hours 4, 6 and 8 were done by a one-way ANOVA. Rates of increases and decreases for each treatment group were compared by use of the X^2 test. Power calculation was not reported.	(39.34±0.27°C); 0.5h; mean T ± SD= 101.7±0.9°F (39.11±0.34°C); 1h; mean T ± SD= 100.9±1.0°F (38.80±0.38°C); 2h; mean T ± SD= 99.8±1.1°F (38.38±0.42°C); 3h; mean T ± SD= 99.5±1.3°F (38.27±0.5°C); 4h; mean T ± SD= 99.5±1.6°F (38.27±0.61°C); 5h; mean T ± SD= 99.8±1.9°F (38.27±0.73°C); 6h; mean T ± SD= 100.2±2.2°F (38.53±0.84°C); 8h; mean T ± SD= 101.2±2.0°F (38.92±0.77°C). <u>Ibuprofen (10mg/kg) n = 25:</u> 0h; mean T ± SD= 102.3±0.8°F (39.34±0.30°C); 0.5h; mean T ± SD= 101.8±0.8°F (39.15±0.30°C); 1h; mean T ± SD= 100.8±0.9°F (38.77±0.34°C); 2h; mean T ± SD= 99.5±0.7°F (38.27±0.27°C); 3h; mean T ± SD= 99.3±0.7°F (38.19±0.27°C); 4h; mean T ± SD= 99.2±1.2°F (38.15±0.46°C); 5h; mean T ± SD= 99.3±1.7°F (38.19±0.65°C); 6h; mean T ± SD= 99.7±1.9°F (38.43±0.73°C); 8h; mean T ± SD= 100.6±2.2°F (38.69±0.84°C). <u>Acetaminophen (10mg/kg) n = 31:</u> 0h; mean T ± SD= 102.5±0.8°F (39.34±0.30°C); 0.5h; mean T ± SD= 101.9±0.9°F (39.19±0.34°C);	of treatment. **Other information** The mean temperature over was plotted versus time for each group.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(39.15°C). High temperature group Age range = 2 to 11years Mean age = 5.5 years Median age = 5.0 years Weight range = 10.8 to 50.5 kg Mean body weight = 21.2 kg Media body weight = 19.6 kg Sex (male n; %) = 21 (40.4%) Diagnosis not reported Mean baseline oral temperature = 103.1°F (39.65°C). **Inclusion criteria** Children age 2 to 11 years, with oral temperature between 101 to 104°F (38.84 to 40°C) were recruited from patients who arrived to a emergency department or clinic and from subject who responded to a newspaper advertisements that asked for volunteers. Or refer by their treating physician. Children were included if they had been scheduled by their treating physician to receive a single oral dose of antibiotics within 2 hours or during the study. **Exclusion criteria** Children that had been treated with antipyretics up to 8 hours before inclusion. Children with pre-study			1h; mean T ± SD= 101.2±0.9°F (38.92±0.34°C); 2h; mean T ± SD= 100.3±0.9°F (38.57±0.34°C); 3h; mean T ± SD= 100.1±1.0°F (38.5±0.42°C); 4h; mean T ± SD= 100.3±1.3°F (38.57±0.5°C); 5h; mean T ± SD= 100.5±1.8°F (38.65±0.69°C); 6h; mean T ± SD= 100.8±1.9°F (38.78±0.73°C); 8h; mean T ± SD= 101.6±1.8°F (39.07±0.69°C). Placebo n =33 0h; mean T ± SD= 102.3±0.8°F (39.34±0.30°C); 0.5h; mean T ± SD= 102.1±0.9°F (39.27±0.34°C); 1h; mean T ± SD= 102.1±0.9°F (39.27±0.34°C); 2h; mean T ± SD= 101.8±1.3°F (39.15±0.5°C); 3h; mean T ± SD= 101.7±1.4°F (39.1±0.54°C); 4h; mean T ± SD= 101.6±1.5°F (39.07±0.57°C); 5h; mean T ± SD= 101.3±1.6°F (38.93±0.61°C); 6h; mean T ± SD= 101.2±1.5°F (38.92±0.57°C); 8h; mean T ± SD= 101.2±1.7°F (38.92±0.65°C). Mean percentage of temperature reduction, 0 to 8 hours : All children Ibuprofen (5mg/kg) : Mean: 460.9 Ibuprofen (10mg/kg) : Mean: 510.8 Acetaminophen (10mg/kg) :	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	salicylate levels >50mg/kg or with acetaminophen levels >5mg/kg. Children with hypersensitivity to aspirin, NSAIDs, anti-inflammatory drugs or paracetamol. History of gastrointestinal conditions. Renal, hepatic, cardiac, malignant, disease. Asthma, diabetes, haematological disorders, diarreha or vomiting within 24 hours before the study. Children that were clinical dehydrated.			Mean: 365.0 Placebo : Mean: 166.5 Low temperature Ibuprofen (5mg/kg) : Mean: 520.7 Ibuprofen (10mg/kg) : Mean: 490.7 Acetaminophen (10mg/kg) : Mean: 441.3 Placebo : Mean: 191.8. High temperature Ibuprofen (5mg/kg) : Mean: 376.3 Ibuprofen (10mg/kg) : Mean: 532.6 Acetaminophen (10mg/kg) : Mean: 272.3 Placebo : Mean: 132.2.	
Full citation Nahata,M.C., Powell,D.A., Durrell,D.E., Miller,M.A., Gupta,N., Efficacy of ibuprofen in pediatric patients with fever, International Journal of Clinical Pharmacology, Therapy, and Toxicology, 30, 94-96, 1992 **Ref Id** 152536 **Country/ies where the study was carried out** USA	**Sample size** n = 56 children Group 1 (Ibuprofen 5mg/kg) = 18 children Group 2 (Ibuprofen 10 mg/kg) = 18 Group 3 Placebo = 20 **Characteristics** Not described in detail **Inclusion criteria**	**Interventions** Group 1 - single dose of liquid ibuprofen at 5 mg/kg Group 2 - single dose of liquid ibuprofen at 10 mg/kg Group 3 - single dose of liquid placebo Rescue if temperature	**Details** **Recruitment** Ethics approval obtained Informed consent obtained **Setting** Not stated	**Results** Initial temperature was 39.2C in ibuprofen groups and 39,4C in placebo. Temperature at 8 hours was 38.3 in group 1, 38.1C in group 2 and 38.9 in group 3. (p<0.05 for ibuprofen vs. placebo). Maximum temperature reduction was at 3 hours for 5 mg/kg (1.3C) ibuprofen and 4 hours to 10 mg/kg (1.8C) and 7 hours for placebo (0.8C). (p<0.05 for ibuprofen vs. placebo).	**Limitations** Limited reporting of patient characteristics Method of randomisation and blinding not described. Data presented in graphical format that cannot be used in meta-analysis. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Randomised controlled trial **Aim of the study** To assess the efficacy of an investigational ibuprofen liquid dosage form in infants and children with fever, using a double-blind, randomised, placebo controlled design. **Study dates** Not reported **Source of funding** The study was supported by Bristol Myers Products, Hillside, N.J	Aged 3 months to 12 years Rectal temperature of 38.3C to 40.5C Indication of need for antipyretics Absence of concomitant drugs or conditions **Exclusion criteria** History of febrile seizures within 6 months Malignant disease Administration of antipyretics within 2 hours or antibiotics between 12 and 60 hours History of hypersensitivity to ibuprofen	increased or above 40.8C	**Allocation** Randomised - but method not stated Blinded - by method not stated **Statistics** ANOVA used to compare mean temperature between groups. **Data collection** Temperature record using calibrated electronic thermometer at 0, 0.5, 1.0, 1.5, 2 to 8 hours Respiration and pulse measured at 1, 2, 4, 6, 8 hours Blood pressure recorded at 2 and 6 hours . Blood samples taken for analysis **Outcomes**		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Difference in temperature. Pharmacodynamics		

2007 Evidence tables

Review question 2

How accurate are the different types of thermometer in the measurement of body temperature in young children and how do they compare in their ability to detect fever?

Review question 3

How accurate are the readings of temperature from different sites of the body in young children and how do these sites compare in the ability to detect fever?

Oral thermometer

Citation/EL	Methods	Results
Bliss-Holtz[36] Study type: Prospective cohort study .El: Ib	Normal healthy 62 girls and 58 boys from 12–48 hrs. Gestational age: 36–42 wk, birth weight: 2570–4900g. Exclusion: 1) Fetal or birth anoxia 2) Have had phototherapy. 3) Received medication apart from Vit K 4) Anomalies or medical conditions that contraindicated with this study. 3 mercury thermometers with calibration. Sites of measurement: oral, axillary and rectal. All the temp. were taken between 1.30–4.00 pm.	The mean difference between AT and OT was 0.6 °F (P< 0.001); between RT and OT was 0.8 °F (P< 0.001); and between RT and AT was 0.2 °F (P< 0.001). The correlation between OT and RT was r = 0.91; between OT and AT was r = 0.81 and between RT and At was r = 0.60. P values were not reported. The largest difference was found between RT and OT. No clear report on the sampling frame and investigator allocation. Did mention that 2 researchers were trained and were responsible for temp. taking. Apgar scores and analgesia were recorded. Also report on the time of temp. reading stabilization. Funding source: Rutgers Graduate College of Nursing.
Banco[33] Study type: Prospective cohort study El: II	They approached 189 parent and 106 infants sucked on pacifiers were recruited including 25 failed to suck consistently for more than 5 minutes and data not extracted due to imperfect use. Inclusion/exclusion: Infants aged 24 months or less presenting to hospital ER between June 86- Jan 87and 56% sucked on pacifiers. Age 10 days to 24 months. 24% infants could not suck consistently for 5 minutes and results were excluded. 10 temperature sensitive pacifiers were bought at the same location at the same time and were used in rotation.	For 81 infants able to suck consistently, 20 had fever (RT > 100 °F, 37.8 °C) and the pacifier thermometer identified 2: sensitivity 10%. After allowing 0.5 °F error (stated by the manufacturer), the 12 infants with 100.5 °F (38.1 °C) and above were separately evaluated, and the pacifier identified 1: sensitivity 8%. No false-positive. A simple but reasonably conducted study. The details of participants and the pacifier thermometer were not given.

Citation/EL	Methods	Results
	Rectal temperature obtained by mercury glass or FILAC digital thermometer. They were previously compared for accuracy, details not provided.	
Talo[73] Study type: Prospective cohort study EL:II	137 children under 18 years. Mean age of rectal/ear group 1.2 years (range 0.08–5.0 years) with 22 females and 21 males. The mean age of the oral and ear group was 9.0 years (range 3–18 years). With 44 females and 50 males. Tympanic temperature recorded with thermoscan (non-corrected). Calibrated.	Correlation for the ear and rectal temperatures was 0.765 (*P*< 0.01). Correlation for the ear and oral temperatures was 0.682 (*P* = 0.01). Single investigator recorded all measurements for one site blinded to results from other sites.
Beckstrand[34] Study type: Prospective cohort study El: II	81 children under 2 years seen in the hospital. Mean age 149 days (ranged from 6 days to 2 years). 1) Tympanic temp. (TT) obtained by Thermoscan Instant. 2) Oral temp. (OT) obtained by Paci-Temp. digital thermometer (dental nipple style only). Rectal temp. (RT) measured by mercury thermometer. Fever: RT > 99.6 °F.	43 (53%) were febrile (RT> 99.6。F). The correlation coefficient between RT and OT was 0.62; while the correlation coefficient between RT and TT was 0.71. Both TT and OT had sensitivity of 63.3% and specificity of 62.8% of detecting fever. All temp. were taken by the same person; children were undressed for the procedure. Manufacturer funded study. Funding source: Supported by the Intelligent Product, Taiwan.
Osinusi[39] Study type: Prospective cohort study El: II	300 children presenting consecutively at a hospital. Malnourished children excluded. Four age groups: neonates, over 1 mth to 1 year, over 1 year to 5 years, and over 5 years to ten years. 75 well children in each group were age and sex matched to 75 febrile children (defined as equal to or greater than the mean rectal temp. of healthy children + 2 standard deviations). Axillary temp. using mercury in glass thermometer.	In both healthy and febrile neonates the difference between the mean rectal and axillary temperatures was not significant (*P*> 0.05). In healthy and febrile children beyond the neonatal period the mean rectal temp. was significantly higher than the mean axillary temp. (*P*< 0.001). The difference between the mean axillary and oral temperature was significant (*P*< 0.001)but there was no significant difference between oral and rectal (*P*> 0.05). Among all children there was a good correlation between the axillary temp. and the rectal or oral (0.89 to 0.99). Among neonates the sensitivity of axillary temperatures for detecting fever was 98% while it was only 47% among older children. The negative predictive value was 98.7% among the neonates and 64.4% among children beyond the neonatal period.

Citation/EL	Methods	Results
Press[251] Study type: Prospective cohort study EL: III	A convenient sample of 100 children were recruited during March 95, Jan-Feb 96. Reasons for disruption not reported. Aged 7–24 months (mean 3.8 months). Enrolled from the paediatric ER.	The mean supralingual temp. (ST): 99.99 °F ± 1.28 °F (97.6–105.4 °F:36.4–40.8 °C). The mean rectal temp. (RT): 100.48 °F ± 1.26 °F (98.0–105.7 °F: 36.7–40.9 °C). The correlation coefficient between supralingual and rectal tem was 0.95. The mean difference between ST and RT (0.49 °F ± 0.42 °F) was significant (*P*< 0.001).The difference between ST and RT with ST adjusted by 0.5F upward (−0.01 °F ± 0.42 °F) was not significant (*P* not reported; 95% CI −0.009 °F to 0.07 °F). 50 had fever (RT) and the pacifier identified 36 (sensitivity 72.0%; specificity 98.0%).When the ST was adjusted by +0.5 °F, it identified 46/50 febrile pt(sensitivity 92.0%; specificity 76.0%)
Jean-Mary[54] Study type: Prospective cohort study EL : III	198 children aged 3 to 36 mths (mean 1.3 years). Presenting at primary care centre. 63 pts considered febrile. 135 afebrile. Children with contraindications to rectal temp. or those with known hypothalamic dysfunction were excluded. Infrared aural temp. in oral mode plus 1F to equate to rectal temp. Infrared axillary temp. plus 1F to equate with rectal temp. Rectal temp. using IVAC digital thermometer.	Axillary thermometer: Sensitivity 63.5%, Specificity 92.6%. Aural thermometer: sensitivity 68.3% specificity 94.8%

Axillary temperature

Systematic review

<table>
<tr><th>Citation /EL</th><th>Method</th><th>Results</th></tr>
<tr><td>Craig[29]

<u>Study Type:</u> systematic review.
Evidence level: 2+</td><td>Aim: To evaluate the agreement between temperature measured at the axilla and rectum in children and young people

Number of People: 37 papers including 5528 children.

Inclusion/exclusion: This study included children 0–18 years and studies using mercury, electronic or thermocouple probes. They excluded children with hypothermia (RT< 35.0 °C), preterm infants (< 37 week gestational age), studies using different devices at the two sites, and mercury thermometer was read before 3 minutes had elapsed.

Studies using mercury, electronic or thermocouple probes measuring AT.

Follow-up period: N/A. Outcome Measures: The difference between AT and RT by mercury, electronic or thermocouple probes</td><td>Effect size:

Mean AT was always lower than mean RT. Significant heterogeneity was found between mean differences and SD within device groups (both mercury thermometer P< 0.001; digital thermometer P< 0.001). The pooled effect using random effect model found that mean differences between RT and AT by mercury thermometer was 0.25 °C (95% limits agreement :−0.15 to 0.65 °C) and 0.58 °C(95% limits agreement :−0.19 to 1.90 °C) for digital thermometer.

When analyse neonate as a subgroup, they found significant heterogeneity between mean differences and SD within groups (Neonates: P< 0.001; older children: P< 0.001). The pooled mean difference between RT and AT by random effect model was 0.17 °C (95% limits agreement: −0.15 to 0.50 °C) for neonates and 0.92 °C (95% limits agreement:m, −0.15 to 1.98 °C).

Reviewer’s comments:

Including children from 0–18 years. No report on the test of sensitivity by fitting into fixed effect model; no justification of the choice of random effect model. Statistical heterogeneity within device groups.

The authors’ conclusion:

In children and young people AT does not agree with RT sufficiently in clinical situations where accurate measurement is important.

In general, limits of agreement were narrower when mercury thermometers were used and placement was longer and in neonates.

<table>
<tr><th>Authors</th><th>No of patients</th><th>Age range (mean)</th><th>Population</th><th>Calibration</th><th>Rectal device, placement time, and depth</th><th>Axilla device (placement time)</th><th>Readings taken</th><th>Intervention between readings</th></tr>
<tr><td colspan="9">Mercury versus mercury thermometer</td></tr>
<tr><td>Akinbami and Sowunmi 1991</td><td>104</td><td>0–48 hours</td><td>Neonates in nursery</td><td>No</td><td>Mercury read at stabilisation (> 7 minutes), 2–3 cm</td><td>Mercury read at stabilisation (> 7 minutes)</td><td>Concurrently</td><td>No</td></tr>
<tr><td>Bliss-Holtz 1989</td><td>120</td><td>12–48 hours</td><td>Infants on radiant</td><td>Yes</td><td>Mercury read at stabilisation (3–</td><td>Mercury read at stabilisation (1–</td><td>Sequentially</td><td>No</td></tr>
</table>
</td></tr>
</table>

Citation /EL	Method	Results								
					warmers		5 minutes), 2.5 cm	7 minutes)		
		Eoff et al 1974	30	1–9 days (3.5 days)	Neonates in nursery	Not stated	Mercury read at 5 minutes, 1.5 cm	Mercury read at 5 minutes	Sequentially	No
		Eoff and Joyce 1981	50	1–6 years	Children in hospital	Not stated	Mercury read at 3 minutes, depth not stated	Mercury read at 5 minutes	Sequentially	No
		Haddock et al 1986	31	24–72 hours	Newborn infants	No	Mercury read at stabilisation (1–6 minutes), 2 cm	Mercury read at stabilisation (3–12 minutes)	Sequentially	No
		Khan et al 1990	30	0–28 days (59 hours)	Neonates in nursery	No	Mercury read at stabilisation (1–5 minutes), 2 cm	Mercury read at stabilisation (1–5 minutes)	Concurrently	No
		Kunnel et al 1988*	99	1–4 days	Neonates in nursery	Yes	Mercury read at optimal temperature over 15 minutes, 2 cm	Mercury read at optimal temperature over 15 minutes	Concurrently	No
		Mayfield et al 1984*	99	1–10 days (4 days)	Newborn infants in nursery	Yes	Mercury read at stabilisation (1–10 minutes), 2 cm	Mercury read at stabilisation (2–10 minutes)	Concurrently	No
		Morley et al 1992*	937	0–6 months	Babies at home and in hospital (11% febrile)	Not stated	Mercury read at ≥ 1 minute or at stabilisation, 3 cm	Mercury read at ≥3 minutes	Not stated	Not stated
		Schiffman 1982	46	1 day (3 hours and 43 minutes)	Neonates in nursery	Yes	Mercury (10 minutes), depth not stated	Mercury read at 10 minutes	Sequentially	No
		Electronic versus electronic thermometer								

Citation /EL	Method	Results								
		Barrus 19831	50	2–6 years	Children in hospital paediatric unit	Yes	Electronic, mode and depth not stated	Electronic, mode not stated	Sequentially	No
		Cusson et al 1997*	63	> 1 hour	Newborn infants in nursery (22% in incubators, 32% on radiant warmers)	Yes	Electronic, predictive mode, 2.5 cm	Electronic, predictive mode	Sequentially	No
		Eoff et al 1974w3	30	1–9 days (3.5 days)	Neonates in nursery	Not stated	Electronic telethermometer, depth not stated (5 minutes)	Electronic telethermometer, read at 5 minutes	Sequentially	No
		Jones et al 1993	573 (sick) and 203 (healthy)	< 5 years in both groups	Sick children in outpatient clinic (31% febrile) and healthy children at home	Not stated in either study	In both groups: electronic, mode not stated, 2.3 cm	In both groups: electronic, mode not stated	Concurrently in both groups	No in both groups
		Martyn et al 1988*	70	1–5 years (33.2 months)	Well children in clinic (31% febrile)	Yes	Electronic, mode and depth not stated	Electronic, mode not stated	Sequentially	No
		Muma et al 1991	224	< 3 years (12.4 months)	Infants and children in casualty department (39% febrile)	Yes	Electronic, mode and depth not stated	Electronic, mode not stated	Sequentially	Not stated

Citation /EL	Method	Results							
		Ogren 1990	61	0–14 years, most < 3 years	Children in casualty department (61% febrile)	No	Electronic read at beep, mode and depth not stated	Electronic read at beep, mode not stated	Not stated	Not stated
		Shann and Mackenzie 1996	100	0–14 years	Children in hospital	Yes	Electronic read at one minute, mode not stated, 2, 3, or 4 cm (according to age)	Electronic read at one minute, mode not stated	Sequentially	No
		Weisse et al 1991	311	0–48 months	Children in inpatient and outpatient settings (21% febrile)	Yes	Electronic read at beep, mode not stated, 2–3 cm	Electronic read at beep, mode not stated	Sequentially	Not stated
		* Studies in which standard deviation of differences in temperature was estimated.								

Citation/EL	Method	Results
Morley[35] Study type: Prospective cohort study EL: Ib	They compared axillary temp. (AT) measured by mercury thermometer with rectal temperature. 289 infants enrolled randomly from birth registry and seen at home during the first 6 months. Another 709 infants with similar age were enrolled when they presented to the hospital. 27 were seen in Cambridge and 682 seen in the Royal Children Melbourne. Inclusion/exclusion: Full term infants randomly selected from the birth registry. This was part of a much larger study to determine the importance of symptoms and signs in babies < 6 mo.	Of 298 babies seen on a random basis at home 281 had both rectal temp. (RT) and axillary temp. (AT) measured. The mean (SD) difference between AT and RT at home was 0.8 (0.5) °C, and 0.6 (0.4) °C at hospital; 0.7 (0.5) °C for combined. Bland-Altman analysis for the difference between each pair of readings. This analysis doesn't assume that one measurement is better than the other. The difference was poorly correlated with the height of BT (more than +2SD of the home babies, i.e. RT> 37.9 °C or AT> 37.2 °C) both at home (r = −0.13) and in hospital (r = 0.21). There is no 'gold standard ' for measuring temp. by this analysis, but RT was found to be a more precise measurements because: 1) RT has smaller SD; 2) the higher temp. is more likely than a lower temp. to be nearest the true BT, and RT was higher than AT in 98% (971/937) cases. At home, AT had a sensitivity of 25% (2/8) , positive predictive value 33 % and 75% false negative to detect fever (> 38.0 °C). When to confirm normal RT, AT had specificity of 99%, negative predictive value 98% and false negative 1%. In hospital, At home, AT had a sensitivity of 73% , PPV 69 % and 27% false negative to detect fever (> 38.0 °C). When to confirm normal RT, AT had specificity of 94%, negative predictive value 96% and false negative 6%. The difference between AT and RT can vary up to 3 °C and it is not possible to adjust AT to RT simply by adding SD. If AT is used to screen high temp. it will miss a quarter of the febrile babies. Well analyzed study with robust statistics. Trained nurses using mercury thermometers measuring both RT and AT.
Bliss-Holtz[36] Study type: Prospective cohort study EL: Ib	normal healthy 62 girls and 58 boys from 12–48 hrs. Gestational age: 36–42 wk, birth weight: 2570–4900g. Exclusion: 1) Fetal or birth anoxia 2) Have had phototherapy. 3) Received medication apart from Vit K 4) Anomalies or medical conditions that contraindicated with this study. 3 mercury thermometers with calibration. Sites of measurement: oral, axillary and rectal. All the temp. were taken between 1.30–4.00 pm.	The mean difference between AT and OT was 0.6 °F (P< 0.001); between RT and OT was 0.8 °F (P< 0.001); and between RT and AT was 0.2 °F (P< 0.001). The correlation between OT and RT was r = 0.91; between OT and AT was r = 0.81 and between RT and At was r = 0.60. P values were not reported. The largest difference was found between RT and OT. No clear report on the sampling frame and investigator allocation. Did mention that 2 researchers were trained and were responsible for temp. taking. Apgar scores and analgesia were recorded. Also report on the time of temp. reading stabilization. Funding source: Rutgers Graduate College of Nursing.
Shann[37] Study type: Prospective cohort	120 inpatients, 20 patients in each of six age groups (< 1 month, 1 to 5 months, 6 to 11 months, 12 to 23 months, 2 to 14 years, and adults. Axillary temperature taken with electronic thermometer	In infants younger than 1 month the difference between the axillary and rectal temperatures varied with age. Least square linear regression analysis showed that the RT was equal to the AT + 0.2 °C for each week of age up to 5 weeks. In the 100 patients older than 1 month the mean (SD) difference between RT and AT was 1.04 °C (0.45 °C). Therefore in all subsequent calculations the axillary temperature was adjusted by adding 1 °C. Bland Altman analysis: Mean difference AT +1 °C – RT = −0.04 95% limits of agreement = −1.1 to 1.0. mean difference Fever

study EL: II	and glass thermometer both calibrated. Forehead skin temperature was taken with three types of strip thermometers (Fever scan Fever monitor and Clinitemp).	monitor – RT = 0.18 95% limits of agreement = −1.3 to 1.7. Mean difference Feverscan – RT = −0.14 95% limits of agreement = −1.5 to 1.3.
Saxena[38] <u>Study type:</u> Prospective cohort study EL :II	100 children between the ages of 3 and 12 years presenting to emergency department. Inclusion/exclusion: middle ear conditions, intense crying or severe sweating of the subjects. Tympanic temperature using Thermoscan Pro 1 in oral mode (this corresponds directly to the ear mode in this thermometer.)	Bland Altman test. Mean difference rectal – right axilla = 1.01 °C (range −0.6 °C to 2.8 °C). Mean difference rectal-left axilla = 1.09 °C (range −0.8 °C to 3.1 °C). Mean difference rectal -right tympanic = 0.56 °C (range −0.4 °C to 2.0 °C). Mean difference rectal – left tympanic = 0.54 °C (range −1.3 °C to 2.9 °C). Our experience is similar to that of other centres that the tympanic thermoprobe is a simple, fast and reliable device for measuring core temperature. The ambient temperature was kept constant by using the same room for all the examinations. Three readings were obtained for each site and the average temperature recorded. Other authors have recommended taking the maximum temperature for tympanic because it is possible to underestimate tympanic temperature but not to over-estimate it.
Osinusi[39] <u>Study type:</u> Prospective cohort study EL :II	300 children presenting consecutively at a hospital. Malnourished children excluded. Four age groups: neonates, over 1 mth to 1 year, over 1 year to 5 years, and over 5 years to ten years. 75 well children in each group were age and sex matched to 75 febrile children (defined as equal to or greater than the mean rectal temp. of healthy children + 2 standard deviations). Inclusion/exclusion: Axillary temp. using mercury in glass thermometer.	In both healthy and febrile neonates the difference between the mean rectal and axillary temperatures was not significant (P> 0.05). In healthy and febrile children beyond the neonatal period the mean rectal temp. was significantly higher than the mean axillary temp. (P< 0.001). The difference between the mean axillary and oral temperature was significant (P< 0.001)but there was no significant difference between oral and rectal (P> 0.05). Among all children there was a good correlation between the axillary temp. and the rectal or oral (0.89 to 0.99). Among neonates the sensitivity of axillary temperatures for detecting fever was 98% while it was only 47% among older children. The negative predictive value was 98.7% among the neonates and 64.4% among children beyond the neonatal period. Unlike in older children axillary temp. in neonates correlates well with the core temp. and it is sensitive enough to detect fever. Axillary temp. rather than rectal temp. should be taken in neonates, while rectal or oral temps should be taken in older children. When the axillary route is used the thermometer should be left in place for at least ten minutes.
Muma[40] <u>Study type:</u> Prospective cohort study EL :II	224 children < 3 years presenting to ED. Inclusion/exclusion: Children who were immunocompromised, were receiving chemotherapy, or had rectal trauma, infection, or anomalies were excluded. Comparison of Rectal, Axillary (both using Diatek 500 electronic thermistor probe) and Tympanic membrane Temperatures (using FirstTEMP- rectal mode). Calibrated.	Mean age 12.4 mths (SD 9.03). Mean RT 38.0ºC, Mean AT 36.48ºC, Mean TMT 37.29ºC. Mean temperature differences between sites RT-AT 1.52 (0.67), RT-TMT 0.71 (0.62), AT-TMT 0.81 (0.74). For all mean differences P< 0.01. Correlation RT versus TMT: r = 0.81, P = 0.001. Correlation RT versus AT: r = 0.75, P = 0.001. Sensitivity of TMT to fever (Rectal temp. 38ºC or more) 55%, specificity 100%. Sensitivity of AT to fever 48%, specificity 96%. The poor sensitivity for tympanic membrane temperature may be due to the size of the probe (8 mm diam) which is twice the size of a paediatric ear speculum. Conclusion: Both TMP and AT temperatures should be viewed with

		caution in children < 3 years old who present to the ED as neither is able to reliably detect fever in this group.
Chaturvedi[41] Study type: Prospective cohort study EL :II	100 infants less than 1 year. 100 children (6–12 years) which is not relevant to this guideline and will not extract information from this group. Excluded LBW infants. Mean age 4.3 m, 47 neonates (< 1 m). 55% female 45% male. Axillary temp.: standard mercury oral thermometer was placed in the axilla with the bulb of the oral thermometer in the right or left posterior sublingual pockets.	Mean RT was 37.5 °C (SD: 0.8 °C) and AT was 37.1 °C (SD: 0.7 °C). The mean difference between RT and AT was 0.3 °C (SD: 0.2 °C) with agreement limits of −0.8-0.76 °C. There was a significant relationship between RT and AT (r = 0.95, P = 0.01) by Bland-Altman method. AT is a good predictor of RT. This study excluded uncooperative and crying children made this study subject to sampling bias.
Anagnostakis[42] Study type: Prospective cohort study EL : II	Total of 1149 of febrile (n = 02) and afebrile (n = 847) children were included. Inclusion/exclusion: Children aged 0–5 years. The afebrile children were recruited from: 1) healthy neonates in the nursery; 2) health children in the well baby clinic and 3) health babies attending kindergarten housed in the hospital. Axillary temp. (AT) measured by mercury thermometer (River Stone G.T 1). Rectal temp. (RT) measured by mercury thermometer (River Stone G.T 1). Definition of fever: RT ≥38.0 °C.	The differences between RT and AT were not significant in the morning (P = 0.91), and the afternoon (P = 0.11) but was borderline significant at midday (P = 0.047). In febrile children, the differences of AT and RT was significantly greater at the onset of fever (P< 0.001) than later, when the fever had been present for at least 2 hr. The mean differences (± SD) between RT and AT are: Morning: 0.62 ± 0.81 °C Midday: 0.61 ± 0.27 °C Afternoon: 0.67 ±0.34 °C. No standard formula can be used to convert AT to RT and vice versa. When it is necessary to take children's temp., RT should be used. Sampling frame of the febrile children was not described. Single investigator took all temp. Temp. was taken under 'basal' condition (i.e. rest for 30 minutes before the measurement), other factors may impact on BT (e.g. crying) were also recorded. Temp. was taken before any antipyretics; children with established fever at the entrance of the study were excluded. The presentation of children with onset of fever (n = 113) and established fever (n = 189) was not clear.
Jirapaet[43] Study type: Prospective cohort	57 neonates from newborn nursery. Age 37 to 42 weeks. Axillary temperature using glass thermometer. Abdominal skin temperature using electronic	Bland Altman: Mean of differences Rectal-Axillary = 0.09 (95% CI 0.06 to 0.12) Rectal-abdominal skin 0.2 (95% CI 0.15–0.26) Rectal-tympanic lying-on ear = 0.52 (95% CI 0.46–0.60). Rectal -exposed ear = 0.21 (95% CI 0.14–0.29). Mean placement time of axillary thermometer for stabilisation = 7.9minutes.

study EL : II	thermometer. Tympanic temp. using infrared tympanic thermometer (First temp. genius 3000A) in rectal equivalency mode. All calibrated	Axillary temperature is as accurate as the rectal temperature measured with a glass thermometer if placement times are optimal. The abdominal temperature may be substituted by adding 0.2 °C. Temperatures obtained with an infrared tympanic thermometer in the rectal equivalent mode with the present probe size are not recommended to substitute for rectal temperatures in neonates. The tympanic thermometer probe was 7.4 mm compared with approximately 4 mm diameter of newborn ear canal. It is therefore likely that this probe size would not measure infrared heat emitted from tympanic membrane. Researchers took the mean of three tympanic measurements when the maximum would have been more appropriate.
Falzon[44] Study type: Prospective cohort study EL: II	Children admitted to the paediatric ward were recruited. 225 were under 4 (paired rectal temp. (RT) and axillary temp. (AT) measured by digital electronic thermometer (Omron MC-3B; Matsusaka Co.) and 112 were 4 years or more (paired oral temp. (OT) and AT). Inclusion/exclusion: Aged 0–14 years, regardless of reasons of admission.	RT and OT correlated with AT (OT: r = 0.62, P< 0.001; RT: r = 0.73, P< 0.001). AT were consistently lower than RT or OT. The mean differences between OT and AT: 0.56 °C, SD: 0.76 °C. The mean differences between RT and AT: 0.38 °C, SD: 0.76 °C. The difference ranged from a mean of 0.4 °C at normothermia (36.5–37.5 °C), and increased to a mean of > 1 °C at RT/OT of > 39.0 °C. These differences were not influenced by clothing. Poor agreement between OT/RT and AT. As pt became increasingly febrile, both RT/OT and AT rose, but the rise of RT/OR was higher than the AT. AT in young children do not reliably reflect OT/RT and should be interpreted with caution. Nurses on duty were allocated to take paired temp. without blinding the results. Clothing and ward ambient temp. were recorded. Funding source: Glaxo Smithkline provided all the instruments.
Zengeya[45] Study type: Prospective cohort study EL: II	They recruited total of 83 children with 166 pairs of data. Inclusion/exclusion: Children admitted to the hospital aged between 3 months to 6 years (medium 12 months). Inclusion of afebrile: 1) fever was denied by guardian; 2) no illness related to fever; 3)RT < 38.0 °C. Gp1: Febrile; Axillary mercury + Tempa Dot vs. Rectal mercury, n = 22. Gp2: Afebrile; Axillary mercury + Tempa Dot vs. Rectal mercury, n = 20	The sensitivity of AT measured by mercury thermometer was 58% (25/43) and the specificity was 100% (40/40; from Gp2&4). The sensitivity of AT measured by Tempa Dot was 68% (15/22; from Gp1&3) and the specificity was 95% (19/20). The sensitivity of AT measured by digital thermometer was 52% (11/21) and the specificity was 100% (20/20). In both febrile and afebrile children, the Tempa Dot and digital thermometers gave higher readings. The RT was significantly higher than AT (P not given), and the mean difference ranging between 0.2–0.7 °C in all four groups. The AT measured by the Tempa Dot, digital or mercury thermometers are poor alternatives to RT measured by mercury thermometer in the diagnosis of fever. No clear description about the sampling frame and the investigator(s) allocation. Author's concluded that there is no standard formula can be used to convert AT to RT and vice versa. When it is necessary to take children's temp., RT should be used.

	Gp3: Febrile ;Axillary mercury + digital vs. Rectal mercury, n = 21 Gp4: Afebrile; Axillary mercury + digital vs. Rectal mercury, n = 20.	
Anagnostakis[42] <u>Study type:</u> Prospective cohort study EL: II	1149 of febrile (n = 302) and afebrile (n = 847) children were included. Children aged 0–5 years. The afebrile children were recruited from: 1) healthy neonates in the nursery; 2) health children in the well baby clinic and 3) health babies attending kindergarten housed in the hospital.	The differences between RT and AT were not significant in the morning (*P* = 0.91), and the afternoon (*P* = 0.11) but was borderline significant at midday (*P* = 0.047). In febrile children, the differences of AT and RT was significantly greater at the onset of fever (*P*< 0.001) than later, when the fever had been present for at least 2 hr.
Akinbami[46] <u>Study type:</u> Prospective cohort study EL: II	They recruited 104 infants, 60 girls and 44 boys. Inclusion/exclusion: Healthy full term infants born with the first 48 hr in the hospital from January to March 1988. Appropriate weight to gestational age. They compared AT measured by mercury thermometer with RT measured by mercury thermometer. Definition of fever: RT ≥38.0 °C.	There was a positive relationship between RT and AT at every minute (*r* = 0.9, *P* not reported). The difference between mean RT (36.76±0.42 °C) and AT (36.68±0.38 °C) was not significant (*P*> 0.05). No report on whether included babies born during the first hour of life. The authors concluded that more frequent use of AT for Nigerian newborns for routine measurements.
Haddock[47] <u>Study type:</u> Prospective cohort study EL: III	A total of 119 RT-AT pair and 54 AT-RT pair were obtained from 173 children. 94 boys and 79 girls. Aged from 7 days to 16 years. Inclusion/exclusion: 1. Children from 0–16 years. 2. For RT: no medical condition that would prohibit RT 3. For OT: parent's belief that child is mature enough to handle OT.	There was 1.2 °F (SD not reported) difference between the mean afebrile OT and AT and 2.2 °F (SD not reported) difference between the mean afebrile RT and AT. For febrile temp.; There was 2.0 °F (SD not reported) difference between the mean OT and AT and 2.8 °F (SD not reported) difference between the mean RT and AT. The combined difference was 1.0 °F (SD not reported) between OT and AT and 2.0 °F (SD not reported) between the RT and AT. The sensitivity of AT ≥99.0 °F of detecting rectal fever was 19.2%, and 50.0% for oral fever; the combined data showed an overall 27.8% sensitivity. No report on sampling frame and investigator allocation. No subgroup analyses.

	AT by Filac F 1010 electronic thermometer (Filac F 1010 Electronic Thermometer). OT/RT measured by the same thermometers. Fever was defined as RT ≥100 °F, OT ≥99.6 °F or AT ≥99.0 °F.	Authors' conclusion: The AT has low sensitivity and should not be relied on to detect fever in infants and children.
Lodha[48] <u>Study type:</u> Prospective cohort study EL: III	They recruited 81 infants (49 boys and 32 girls) presenting to the paediatric ward, out-patient department and ER. Inclusion/exclusion: Infants < 1yr were recruited. Mean age 5.3 months. 30% sought care for fever alone, 16% had lower respiratory infection, and 25 had upper respiratory infection. Exclusion: prematurity, localised infection, peripheral circulation failure or diarrhoea. Axillary temp. (AT) measured by mercury glass thermometer. Rectal temp. (RT) measured by mercury glass thermometer.	The mean RT was 38.4 °C±1.1 °C (36.0–40.7 °C), the mean AT was 37.9 °C±1.0 °C (36.0–40.5 °C). The mean difference between RT and AT was 0.6 °C±0.4 °C (−0.5 to 2.0 °C). The correlation between RT and AT was 0.93, *P* value not reported. AT+0.6 °C had sensitivity of 98% and 90% specificity detecting rectal fever (RT ≥38.0 °C). Data on children 6–14 years comparing AT to OT was not extracted. Nutritional status and diagnosis were recorded. Sampling frame and investigator (n = 2) allocation were not stated. Author's conclusion: AT is an acceptable alternative to RT.
Buntain[49] <u>Study type:</u> Prospective cohort study EL: III	69 pt (have illness) had RT and AT measured by mercury thermometer; another 36 babies (status not clear) had RT and AT measured by flexible Diagnostic Electronic Thermometer (Diagnostic Inc.). I69 babies had some specific or surgical problems, detail not provided; and the other 36 babies' condition not reported. AT measured by mercury thermometer and flexible Diagnostic Electronic Thermometer (Diagnostic Inc) in 2 separate groups of babies.	The AT measured by mercury thermometer was taken at 3,5 and 10 minutes, and the digital readings were taken at the time of maximal rise of the indicator. The correlation coefficients (*r*) between RT and AT (mercury) were: 0.67 at 3 minutes; 0.71 at 5 minutes and 0.76 at 10 minutes (all *P*< 0.001). The correlation coefficient (*r*) between RT and AT measured by digital thermometer was 0.56, *P*< 0.001. No report on subject's age and other info. No sampling frame and info about the allocation of the investigators. Author's conclusion: The correlation of AT and RT is close when mercury thermometer was used, the longer the time in obtaining the AT, the better the correlation.

	RT measured by mercury thermometer and flexible Diagnostic Electronic Thermometer (Diagnostic Inc) in 2 separate groups of babies.	
Ogren[56] Study type: Prospective cohort study EL: III	Total of 159 children.82 boys and 74 girls; 54 were < 3yr. Inclusion/exclusion: all children aged < 14 years presenting to the ER during 18 July to 5 September, 1988. AT measured by Diatek 600 digital thermometer (Diatek Inc.)	Together 103 OT-AT pairs and 61 RT-AT pairs. There were 2 pt less than 3 years capable of taking OT. There were 71 OT-AT pairs and 24 RT-AT pairs were afebrile. The mean afebrile AT was 36.1 °C (SD:0.67 °C), the mean+2SD = 37.4 °C was tested of its predictive value of combined rectal/oral fever. The sensitivity was 46% (32/69), specificity 99% (94/95), positive predictive value 97% (32/33), and the negative predictive value was 72% (94/103). The results remain unchanged when they calculate RT and OT separately. The correlation coefficient between OT and AT was 0.74, and 0.70 for OT and RT (*P* value not provided). OT was 1.17 °C (SD:0.72 °C) higher than AT; and the RT was 1.80 °C (SD:0.97 °C) higher than AT. No report on age break down and the allocation of the investigators. No statement about the exclusion and other characteristics of the subjects.
Barrus[51] Study type: Prospective cohort study EL: III	50 hospitalised children. Inclusion/exclusion: Mean age 2–6 years. 19 girls and 31 boys. AT measured by the IVAC 821 digital thermometer.	The mean difference between RT and AT was 0.42 °C (SD:0.54 °C) ranged from −0.9 to 1.8 °C. There was significant correlation between RT and AT (r = 0.62, P< 0.001). It is encouraged to health professionals to take AT whenever possible. Manufacturer funded study. No clear description about the subjects' clinical condition. Convenient sample. The sample had lower percentiles of height and weight than average. Funding source: IVAC Corporation.
Weisse[52] Study type: Prospective cohort study EL: III	Population size: 114 form from well baby clinic aged 2wk to 18 months ; 115 from acute care, and 42 aged 1–48 months on the inpatient service. Inclusion/exclusion: Children presenting to the paediatric service from Oct 1988 to April 1999 were recruited. Axillary temp. (AT) measured by the electronic thermometer (IVAC Corp.)	The mean difference between AT and RT was 0.8–1.0 °C. Using AT > = 37.0 °C has 94% sensitivity detecting fever in acute care; and 93% for hospitalised pt. AT is impractical for use as a screening test for fever because of poor sensitivity and high rate of false positive. When a child presents to a clinic or is admitted to the hospital with a complaint or history of fever, AT should not be used. The order of AT/RT measurements was randomly allocated at admission, form of randomization not reported. Not report on the disease profile of the participants.
Brown[53]	49 simultaneous recordings were made from 10	The mean (SD) of the AT was 36.6 (0.38) °C and RT 37.5 (0.25)°C. The correlation between RT and AT was poor

Study type: Prospective cohort study EL: III	infants during hospitalisation. Those who were considered as afebrile by the clinicians were included. Axillary temp. (AT) measured by the mercury thermometer.	(*r* = 0.48, *P* not reported). When plotting the differences between the methods against their means, they found that there was a wide scatter of the plots around the mean difference. Moreover, the agreement ranged from 0.2–1.6 °C difference. These data indicated that in infants, the AT doesn't accurately reflect RT in either consistent or reliable fashion. AT does not reflect OT consistently and reliably. If infant body temp. is sought, a RT should be used. Study based on only small number. The sampling frame was not reported. The authors referred to one study reporting the accuracy of the electronic rectal probe. Funding source: Canterbury cot death fellowship.
Jean-Mary[54] Study type: Prospective cohort study EL : III	198 children aged 3 to 36 mths (mean 1.3 years). Presenting at primary care centre. 63 pts considered febrile. 135 afebrile. Children with contraindications to rectal temp. or those with known hypothalamic dysfunction were excluded. Infrared aural temp. in oral mode plus 1F to equate to rectal temp. Infrared axillary temp. plus 1F to equate with rectal temp. Rectal temp. using IVAC digital thermometer.	Axillary thermometer: Sensitivity 63.5%, Specificity 92.6%. Aural thermometer: sensitivity 68.3% specificity 94.8% For a visit in an outpatient setting the use of either of these devices (infrared axillary or aural thermometers) is an appropriate screening tool. But if history or physical examination raise concern for possible febrile illness, the rectal value should be used for the purpose of clinical accuracy.

Chemical dot/TempaDot

Citation/EL	**Method**	**Results**
Leick-Rude[60] Study type: Prospective cohort study EL II	208 sets of data were obtained from a convenient sample of 220 infants weighing > 1500 g in level III NICU. The population consisted of term and preterm infants with a wide variety of medical and surgical conditions. Infants aged from 1–102 days (mean 17.2, SD:21.8 days). Excluded were infants with skin conditions that would prevent application of patches or any other conditions for which use of the other instrument was inappropriate. Axillary temperatures obtained by mercury thermometer compared with those obtained by TempaDot, B-D digital thermometer, Mon-a-therm infant temperature sensor and incuTemp3 radiant warmer skin temperature sensor and	TempaDot axillary measurements correlated well with mercury thermometer. TempaDot averaged 0.39 °c higher (SD:0.27 °c) above the mercury thermometer; 95% were within a difference of −0.15 °C and 0.93 °C, and 73.2% were with ±0.05 °C. TempaDot showed greater difference at lower mercury temperatures.

Citation/EL	Method	Results
	IVAC.CORE tympanic thermometer,	
Morley[59] <u>Study type:</u> Prospective cohort study EL : II	1090 children presenting to a hospital and on a children's ward. Median age 2 years. Range 1 month to 16 years. Tempa-DOT in axilla. Fever scan on forehead. Fever defined as 38 °C.	Feverscan-mercury measuring axillary temp. Correlation coefficient 0.7319. Mean difference = 0.27 °C (SD 0.80). Sensitivity 89% (243/274). PPV 57% (243/425). Specificity 78% (628/810) NPV 95% (628/659). TempaDot-mercury measuring axillary temp.: Correlation coefficient 0.9217. Mean difference 0.32 °C (SD0.45). Sensitivity 92% (252/293) Specificity 95% (771/812) NPV 95% (628/659). Both FeverScan and Tempa-DOT are sensitive at detecting fever in children, although FeverScan seriously overdiagnoses fever by 74%. The positive predictive value for accurately detecting fever was only 57% for FeverScan and 86% for Tempa -DOT.
Zengeya[45] <u>Study type:</u> Prospective cohort study EL: II	They recruited total of 83 children with 166 pairs of data. Children admitted to the hospital aged between 3 months to 6 years (medium 12 months). Inclusion of afebrile: 1) fever was denied by guardian; 2) no illness related to fever; 3)RT < 38.0 °C. Gp1: Febrile; Axillary mercury + Tempa Dot vs. Rectal mercury, n = 22. Gp2: Afebrile; Axillary mercury + Tempa Dot vs. Rectal mercury, n = 20 Gp3: Febrile ;Axillary mercury + digital vs. Rectal mercury, n = 21 Gp4: Afebrile; Axillary mercury + digital vs. Rectal mercury, n = 20.	The sensitivity of AT measured by mercury thermometer was 58% (25/43) and the specificity was 100% (40/40; from Gp2&4). The sensitivity of AT measured by Tempa-Dot was 68% (15/22; from Gp1&3) and the specificity was 95% (19/20). The sensitivity of AT measured by digital thermometer was 52% (11/21) and the specificity was 100% (20/20). In both febrile and afebrile children, the Tempa Dot and digital thermometers gave higher readings. The RT was significantly higher than AT (*P* not given), and the mean difference ranging between 0.2–0.7 °C in all four groups. The AT measured by the Tempa-Dot, digital or mercury thermometers are poor alternatives to RT measured by mercury thermometer in the diagnosis of fever. No clear description about the sampling frame and the investigator(s) allocation.

Forehead thermometer

Citation/EL	Method	Results
Shann[37] Study type: Prospective cohort study EL: II	120 inpatients with 20 patients in each of six age groups (< 1 month, 1 to 5 months, 6 to 11 months, 12 to 23 months, 2 to 14 years, and adults. Axillary temperature taken with electronic thermometer and glass thermometer both calibrated. Forehead skin temperature was taken with three types of strip thermometers (Fever scan Fever monitor and Clinitemp).	Bland Altman analysis found that the mean difference between Fever monitor – RT = 0.18 95% limits of agreement = −1.3 to 1.7. Mean difference Feverscan – RT = −0.14 95% limits of agreement = −1.5 to 1.3.
Scholefield[62] Study type: Prospective cohort study EL: II	134 patients coming to the clinic for either well-child care or acute illness between May 1980 to Jan 1981. Mean age : 4 years (12 days to 17 yrs).64% received medicine. The pt closely resembled the clinical population in racial composition, language and proportion receive Medicaid. Forehead temp. measured by 3 successive times using either the 3 Clinitemps (Clinitemp Inc.) or 3 Fever Scans (American Thermometer Co.) (purchased from pharmacies). Either rectal temp. (RT; < 4 years) or oral temp. (OT; > 4yr) measured by mercury glass thermometer. Definition of fever: RT ≥ 38.0 °C or OT ≥ 37.4 °C. Serious fever: RT ≥ 38.9 °C, OT not included for this analysis.	FT by Clinitemp was different from either RT (*P*< 0.005) or OT (*P*< 0.005). FT by Fever Scan was different from either RT (*P*< 0.005) or OT (*P*< 0.005). The Clinitemp identified 27% (9/33) fever and 9% (1/11) serious fever. 71.4% (5/7) children < 2 years with 38.9 °C or more (RT) were identified as afebrile by Clinitemp. The Fever Scan identified 79% (26/33) fever and 33% (4/12) serious fever. 16.7% (1/6) children < 2 years with 38.9 °C or more (RT) were identified as afebrile by Fever Scan. The breaking down of the percentages and details of pt using either Clinitemp or Fever Scan not reported.
Schuh[84] Study type: Prospective cohort study. EL:	Population size: 332 parents with children under 2 years were included, and 327 sets of complete data. 313 parents agreed to measure their children's temperature by Temporal Artery Consumer Model (TAMC). Inclusion/exclusion: Mean age: 9.2 months, SD:6.8 months (range 1–24 months).89 (27%) were under 3 months. 94 (29%) took antipyretics 4 hr	TAMP detected 81% (110/136) RT ≥ 38.0 °C, 88% (89/101) RT ≥ 38.3≥C; 82% (41/50) RT ≥39.0≥C. 80.7% . 26 (16.9%) had rectal fever (> 38.0 °C) were afebrile by TA methods. The validity of using this specific model of digital thermometer for RT was not justified. Manufacturer funded study.

Citation/EL	Method	Results
III	before arrival to the ER. Temporal artery (TA) temperature measured by the temporal artery consumer model (TACM, Sensor Touch model HF370, Philips). RT taken by digital thermometer (IVAC 2000, ALARIS Medial Systems) as the standard criterion; and with the TA temperature taken by temporal artery professional model (TAPM; Temporal Scanner model LXTA, Exergen Co.) were the primary outcome .	Funding source: Exergen Corporation.
Valadez[63] <u>Study type:</u> Prospective cohort study EL:III	Population size: 498 children were recruited from 1993–3 (12 months period). Paired temp. were taken by traditional birth attendants (TBA) on 2 separate occasions (45–360 days after the 1st measurement; mean:105.7, SD:28.8). Inclusion/exclusion: Mean age 2–52 months (mean:20.86 D, medium:22, SD:9.5) at the 2nd measurement. Forehead temp. (FT) measured by Liquid Crystal Thermometer (LCT): 4x11 cm with a 3 mm foam backing. RT measured by mercury thermometer. FT and RT were recorded simultaneously	The 1st and 2nd sets of readings showed linear relationship (r = 0.804, 0.834 respectively). The greatest difference in the math model occurred at the lower LCT readings, could be due to mercury thermometers do not read < 35.0 °C. 1st measurement: LCT readings were on average 1.24 °C (SD:0.72 °C; n = 497) lower than RT. 2nd measurement: LCT readings were also on average 1.24 °C (SD:0.75 °C; n = 496) lower than RT. Timing of the 1st measurement not reported. Sampling frame and investigator allocation not described. Loss of follow up was not consistently reported.
Dart[64] <u>Study type:</u> Prospective cohort study	Forehead temp. (FT) measured by the Liquid Crystal Thermometer (Temp. Trend II, Biosynergy Inc.), a disposable, flexible plastic 1.5 cm square backed with adhesion to the forehead. Oral temp. (OT) measured by digital thermometer. The OT was recorded every 15 minutes until	The correlation coefficient between LCT and OT was 0.661 (P< 0.01). Of afebrile pt, 16 (15.6%) were falsely identified as becoming febrile during evaluation. Population had very wide range of age. No attempt to minimise bias. The use of digital thermometer to measure OT as a reference is less robust.

Citation/EL	Method	Results
EL: III	discharge or after 2 hrs.	

Infrared tympanic thermometer

Systematic review

Citation/EL	Method	Results
Craig[30] Study Type: Systematic review and meta-analysis . EL : II	Number of People: 4441 (meta-analysis). Age 0–18 years. Inclusion/exclusion: Children with Hypothermia and preterm infants were excluded. Temperature measured at the ear Outcome Measures: pooled mean temperature difference	The pooled mean temperature difference was 0.29 °C(95% CI −0.74 to 1.34). Data was also pooled by mode (i.e. offset applied to thermometer). Rectal mode mean difference 0.15 °C(−0.95 to 1.25), actual 0.70 °C (−0.20 to1.60), core 0.25 °C (−0.78 to 1.27), oral 0.34 °C (−0.86 to 1.54), tympanic 0.62 °C (−0.40 to 1.64) and mode not stated 0.32 °C (−0.57 to 1.21). Authors' conclusion: Although the mean differences between rectal and ear temperature measurement were small, the wide confidence intervals mean that ear temperature is not a good approximation of rectal temperature, even when the ear thermometer is used in rectal mode. Comments: Study uses Bland-Altman approach which is recommended for method comparison studies. Meta-analysis limited by considerable amounts of heterogeneity with regards to age, calibration, presence of fever, and data collection methods. Source of funding: Grant from the Royal Liverpool Children's NHS Trust Endowment Funds.
Dodd[252] Study Type: Systematic review and meta-analysis . EL II	Aim: To determine the diagnostic accuracy of tympanic thermometers by examining the sensitivity and specificity of the studies found in previous systematic review[30] Method: Of the 44 original studies eligible for the SR, those reported sensitivity and specificity, or whose authors provided individual patient data, were included for this analysis.	23/44 studies were included, giving 4098 children (69%). The diagnostic ORs varied extensively across studies, suggesting heterogeneity between study estimates is not fully explained by the threshold effect. Pooled estimates of sensitivity and specificity from random effect model were 63.7% (95% CI 55.6–71.8%) and 95.2 (93.5–96.9%).

Individual studies

Citation/EL	Method	Results
Kenney[66] Study type: Prospective cohort study EL Ib	964 pts (all pts seen in a general paediatric clinic in 2 mth period). From newborn to 18 years. Half of patients were between 4 and 48 mth old. 32% of patients were older than 48mths and 18% were less than 3 mths. The majority (70%) were afebrile. Tympanic membrane temperature (Firstemp) in rectal and oral modes. A febrile reading in oral mode equalled > 37 °C, on the rectal mode > 37.6 °C.	Tympanic membrane temp. measurements were reproducible. Mean difference between Tympanic membrane thermometer and the glass mercury thermometer was 0.06 °C ± 0.03. Sensitivity 79%, Specificity 74%, PPV 56%, NPV 89%, accuracy 75%. Measurement by tympanic membrane thermometer and glass mercury thermometer were similar in the neonate and older child and in febrile and afebrile temperature ranges. Although clinically accepted, oral or rectal temperatures have been shown to be far from gold standard. We suggest that based on previous reports and physiological anatomical mechanisms involved, tympanic membrane thermometer readings probably reflect the core body temperature more accurately. Verifying this possibility with other standards of central core temperature measurement such as in paediatric cardiac surgery pts requiring thermodilution catheters would provide conclusive evidence.
Akinyinka[67] Study type: Prospective cohort study EL Ib	378 children aged ≤60 months presenting at paediatric emergency and outpatient departments. Tympanic temperature taken using ear tug and Thermoscan Instant Thermometer model 6005. Rectal temperature using rectal mercury thermometer. Data collection was blinded	Mean rectal temperature 37.3ºC (SD = 0.8). Mean aural temperature 37.2ºC (SD = 0.9), *P* = 0.10. The mean difference = 0.09 °C. Bland-Altman 95% limits of agreement −0.747 to 0.930. Pearson's coefficient = 0.838, Lin's concordance correlation coefficient = 0.832. There was no significant difference between age groups. At 37.5ºC Sensitivity was 73.0%, Specificity was 95.0%, PPV was 85.0%, NPV was 90.0%, Accuracy was 88.9%, False positives 7.4%, False negatives 3.7%. Authors conclusion: Tympanic thermometry in our study appeared to perform similarly to rectal temperature. The ease and speed of temperature recording via the aural route makes tympanic thermometry attractive in the typically busy emergency room often seen in the tropics.
Davis[68] Study type: Prospective cohort study EL: II	209 male and female hospitalized subjects free from abnormalities of the external ear, oral cavity, axilla and rectal areas. All other diagnoses were included. Oral, axillary and rectal temperatures measured using an electronic thermometer (diatek 600). Tympanic measurements using infrared	In children aged 1–48 months (n = 66, n measurements = 103) Tympanic-rectal correlation *r* = 0.82, *P*< 0.0001. Sensitivity to fever 90.3%, Specificity 89.3%. Tympanic measures identified fevers more often than oral or axillary measurements. Axillary measurement is useful only in the neonatal period. The training for data collection included tests of inter-rater reliability. All measurements were with 0.2F of the control.

Citation/EL	Method	Results
	tympanic membrane thermometer (first temp.) set on core mode. All calibrated	The study is limited in that rectal measurements were only taken in the 1 to 48mth group (n = 66, n measurements = 103).
Jirapaet[43] <u>Study type:</u> Prospective cohort study EL II	57 neonates from newborn nursery. Age 37 to 42 weeks. Axillary temperature using glass thermometer. Abdominal skin temperature using electronic thermometer. Tympanic temp. using infrared tympanic thermometer (First temp. genius 3000A) in rectal equivalency mode. All calibrated	Bland Altman: Mean of differences Rectal-Axillary = 0.09 (95% CI 0.06 to 0.12) Rectal-abdominal skin 0.2 (95% CI 0.15–0.26) Rectal-tympanic lying-on ear = 0.52 (95% CI 0.46–0.60). Rectal -exposed ear = 0.21 (95% CI 0.14–0.29). Mean placement time of axillary thermometer for stabilisation = 7.9minutes. Axillary temperature is as accurate as the rectal temperature measured with a glass thermometer if placement times are optimal. The abdominal temperature may be substituted by adding 0.2 °C. Temperatures obtained with an infrared tympanic thermometer in the rectal equivalent mode with the present probe size are not recommended to substitute for rectal temperatures in neonates.
Yetman[69] <u>Study type:</u> Prospective cohort study El : II	200 newborn babies in well baby nursery at private teaching hospital. 105 male, 95 female.: Infants having abnormal otic or rectal structures and those infants requiring isolation for infectious diseases were excluded. Tympanic temperature using First temp. Genius 3000A. Oral equivalent and rectal equivalent modes tested. Calibration prior to study and weekly thereafter. Blind study.	The mean difference between tympanic temp. in rectal mode and rectal temp. was 0.3 (P< 0.0001). More than 50% of Tympanic rectal equivalent temps differed from rectal temp. by more than 0.3 °C.
Mayfield[70] <u>Study type:</u> Prospective cohort study EL: II	70 term infants (37 weeks gestation or more). More than 30 days old, evidence of necrotizing enterocolitis, blood in faeces, rectal or anal fissures, or major congenital abnormalities or had been placed in strict isolation were excluded. Tympanic membrane temperature using flexible thermistor probe (YSI 511).	Mean deep rectal temperature was 37.01 ºC (SD = 0.33). Mean tympanic membrane temperature was 36.83 ºC (SD = 0.36). There was a significant correlation (P< 0.001) between measurement sites (r = 0.84).

Citation/EL	Method	Results
	Deep rectal temperature measured using thermistor probe (5 cm beyond the anus)	
Stewart[71] Study type: Prospective cohort study EL: II	79 paediatric patients presenting to an emergency department. Age 3 weeks to 5 years, mean 11.9 months. Tympanic temperature using infrared tympanic thermometer (FirstTemp®) set to core equivalency setting (i.e. thermometer adds 0.9 °C to the tympanic temperature). Rectal temperature measured using electronic digital thermometer.	Mean tympanic temperature was 38.6ºC (SD1.08) mean rectal temperature was 38.8ºC (SD1.02). A highly significant correlation between patient temperatures taken with the tympanic and rectal thermometers was shown (r = 0.93, P< 0.001). The correlation coefficient for patients less than 3 months old (r = 0.64, n = 8) was compared with the correlation coefficients for patients 4 to 12 months old (r = 0.93, n = 46) and more than 12 months old (r = 0.95, n = 25) and found to be significantly weaker (P< 0.01). Of the eight patients in the < 3 month group, four showed identical rectal and core-tympanic temperatures and four had rectal temperatures higher than core-tympanic. Defining fever as a temperature of more than 38.0º C, the overall sensitivity, specificity, positive predictive, and negative predictive values were 96.8%, 100%, 100%, and 90.1% respectively. For patients more than 3 months old, the values were 100% in all categories.
Lanham[72] Study type: Prospective cohort study EL: II	178 children aged ≤6 years. Mean age 18.6 mths (SD = 14.2). According to department protocol, Rectal temp. taken from all patients less than 3 years and patients three to 6 years who presented with a complaint of fever. Tympanic temp. measured using First Temp. Genius (tympanic mode). Calibration ascertained prior to implementation and the completion of the study. Rectal temp. measured using Diatek 600 digital thermometer.	Mean rectal temp. 38.28ºC (SD = 0.86). Mean tympanic temp. 37.08ºC. Mean difference −0.60 (SD = 0.54). Correlation = 0.84, P< 0.001. Sensitivity 51%, Specificity 99%, PPV 99%, NPV 61%. Multivariate regression analysis found age (P = 0.0001), fever (P = 0.00012) and nurse (0.0016) to have a significant effect. As the age of the subject decreased, the rectal-tympanic temperature difference increased. As the rectal reading increased, indicating fever, the tympanic-rectal difference increased.
Saxena[38]	100 children between the ages of 3 and 12 years presenting to emergency department. Children with middle ear conditions, intense	Bland Altman test. Mean difference rectal – right axilla = 1.01 °C (range −0.6 to 2.8 °C). Mean difference rectal- left axilla = 1.09 °C (range −0.8 to 3.1 °C). Mean difference rectal -right tympanic = 0.56 °C (range −0.4 to 2.0 °C). Mean difference rectal – left tympanic = 0.54 °C (range −1.3 to 2.9 °C).

Citation/EL	Method	Results
Study type: Prospective cohort study EL: II	crying or severe sweating were excluded. Tympanic temperature using Thermoscan Pro 1 in oral mode (this corresponds directly to the ear mode in this thermometer.)	Our experience is similar to that of other centres that the tympanic thermoprobe is a simple, fast and reliable device for measuring core temperature. The ambient temperature was kept constant by using the same room for all the examinations.
Muma[40] Study type: Prospective cohort study EL: II	224 children < 3 years presenting to ED. Children who were immunocompromised, were receiving chemotherapy, or had rectal trauma, infection, or anomalies were excluded. Comparison of Rectal, Axillary (both using Diatek 500 electronic thermistor probe) and Tympanic membrane Temperatures (using FirstTEMP- rectal mode). Calibrated.	Mean age 12.4 mths (SD 9.03). Mean RT 38.0ºC, Mean AT 36.48ºC, Mean TMT 37.29ºC. Mean temperature differences between sites RT-AT 1.52 (0.67), RT-TMT 0.71 (0.62), AT-TMT 0.81 (0.74). For all mean differences *P*< 0.01. Correlation RT versus TMT: *r* = 0.81, *P* = 0.001. Correlation RT versus AT: *r* = 0.75, *P* = 0.001. Sensitivity of TMT to fever (Rectal temp. 38ºC or more) 55%, specificity 100%. Sensitivity of AT to fever 48%, specificity 96%. The poor sensitivity for tympanic membrane temperature may be due to the size of the probe (8 mm diam) which is twice the size of a paediatric ear speculum.
El-Radhi[83] Study type: Prospective cohort study EL: II	106 infants attending A&E was measured in daytime using infrared tympanic thermometer. The readings were compared with those obtained from the axilla with an electronic thermometer and the rectum.	The mean difference between tympanic and rectal temperature was 1.11 °C; it has sensitivity of 76%.
Talo[73] Study type: Prospective cohort study EL:III	137 children under 18 years. Mean age of rectal/ear group 1.2 years (range 0.08–5.0 years) with 22 females and 21 males. The mean age of the oral and ear group was 9.0 years (range 3–18 years). With 44 females and 50 males. Tympanic temperature recorded with thermoscan (non-corrected). Calibrated. Single investigator recorded all measurements for one site blinded to results from other sites.	Correlation for the ear and rectal temperatures was 0.765 (*P*< 0.01). Correlation for the ear and oral temperatures was 0.682 (*P*,0.01).
Rogers[74]	108 patients in paediatric unit Age 1 mth to 16	295 paired observations: Tympanic -Rectal n = 32, t = 4.56, *P* = 0.0001. Tympanic-oral n = 65, t = 2.70, *P* = 0.0088.

Citation/EL	Method	Results
<u>Study type:</u> Prospective cohort study EL: III	yrs. Mean age 4 years. Only 2 febrile patients. TM temperature using TM thermometer (First temp.) off-set not stated.	Tympanic-axillary n = 198, t = 8.41, *P* = 0.0001. Correlation: Tympanic-rectal n = 32, *r* = 0.58, *P* = 0.0005, Tympanic-oral n = 65, *r* = 0.52, *P* = 0.0001. Tympanic-axillary n = 198, *r* = 0.41, *P* = 0.0001.
Rhoads[75] <u>Study type:</u> Prospective cohort study EL:III	113 children aged 1 month to 10 years. 65 tympanic-rectal comparison. 48 Tympanic-oral comparison. Tympanic temperature measured using FirstTemp. Offset not stated. Calibration not stated.	Correlation Tympanic-rectal *r* = 0.77, correlation tympanic-oral *r* = 0.75. None of the seven patients with a rectal temperature of 39 °C or more and only 7 of 27 (26%) with a rectal temperature of 38 °C or more were identified. None of three patients with an oral temperature of 39 °C or more and only 10 of 35 (29%) of those with an oral temp. of 38 °C or above were identified.
Pransky[76] <u>Study type:</u> Prospective cohort study EL:III	100 patients aged 7 months to 13 years examined in the private office of a paediatric otolaryngologist. Tympanic temperature measured with Thermoscan Pro 1 with and without ‘ear tug’.	A difference in temperature was obtained when the ear tug was utilized as compared with simply placing the probe tip into the external auditory canal. When the ear tug was not utilised there was a decrease in temperature reading that varied approximately 0.4F(+/- 0.2F, one standard deviation). Using the ear tug compared favourably to the temperature obtained orally. There was no impact by the tympanostomy tubes, a serious otitis media or middle ear effusion, a ‘normal’ mild-moderate amount of cerumen or by small external auditory canals. However tympanosclerosis did seem to reduce temp. compared with oral temp.
Bernardo[77] <u>Study type:</u> Prospective cohort study EL: III	40 children were recruited from the ER. 11 severely and 29 moderately injured children, mean age 6.9 years (SD:4.4 years, range 1–14 years). Exclusion: < 1yr, sustained bilateral haemotympanum, spinal injury, pelvic fracture, rectal trauma, submersion injury, true hypothermia. The Core-Check (infrared) Tympanic Thermometer system 2090 (IVAC Co) was used	The association between aural (AT) and rectal temp. (RT) was moderate to high (*r* = 0.85) by Pearson product-moment corr coef. Mean RT: 36.8 °C (SD:1.4 °C); mean AT: 36.5 °C(SD: 1.3 °C). Mean difference between RT & AT = −0.3 °C, SD:0.76 °C, *P*< 0.05. Authors conclusion: The moderate to high correlation shows promise for use of AT measurements as an initial screening for children with moderate to severe injury. Because of this findings, they changed their practice and wrote a guidelines for use AT as screening tool.

Citation/EL	Method	Results
	to measure aural temp. Rectal temp. measured by the Temp.-Plus II model 2080A (IVAC Co). Accuracy was verified by a prob simulator supplied by the manufacturer. This thermometer was dedicated for use only for this study. The validity of Temp.-Plus II for RT was not discussed and no reference given. No clear attempt to minimise bias. Though the difference between RT & AT was statistically significant(−0.3 °C), the authors stressed on the moderate to high correlation.	
Selfridge[78] <u>Study type:</u> Prospective cohort study EL: III	102 patients presenting at emergency department. Age < 3 months. Tympanic membrane (TM) temperature using First Temp. Model 2000A (oral mode). Calibrated prior to study (but not daily or weekly after that). Rectal temperature using standard mercury glass thermometer	Fever was defined as 99.6º F or greater using TMT thermometer or 100.6º F or greater using rectal thermometer. Sensitivity 88%, specificity 89%, PPV 74% and the NPV 79%.
Brennan[79] <u>Study type:</u> Prospective cohort study EL: III	370 children aged 6 mths to 6 years presenting at emergency department. Mean age 18.4 mths (SD = 11.3). 56% were boys. According to department protocol oral temperature was taken with older, more cooperative patients, these patients were excluded. Rectal temp. taken in younger and less cooperative pts and those with recent oral ingestion.	Rectal temperatures showed good correlation with both right and left TM temp. (r = 0.83 and 0.85, P< 0.001). TM temps were highly correlated with each other (r = 0.91, P< 0.001). Mean rectal temp. 101.0ºF (SD = 2.0), Mean right TM temperature 100.4 ºF(SD = 1.9ºF). Mean left TM temperature 100.3ºF (SD = 1.9). The TM temperatures were significantly lower than rectal readings (P< 0.001). The mean difference was 0.7 ºF (SD = 1.1). Analysis of subgroups failed to find a significant effect of age, gender, cerumen, otis media or technique. Detection of fever: Sensitivity 76.4%, Specificity 92.2%, PPV 92.3%, NPV 76.2%. Detection of high fever: Sensitivity 56.6%, Specificity 98.3%, PPV 89.6%, NPV 89.8%.

Citation/EL	Method	Results
	Tympanic membrane (TM) temperature measured using First Temp. (measurements converted to rectal mode). All equipment calibrated weekly. Rectal temperature measured using electronic thermistor thermometry (IVAC 160EE).	
Loveys[80] <u>Study type:</u> Prospective cohort study EL: III	140 children aged 0–2 years hospitalised at an infant and toddler unit. Children who were neutropenic, had an imperforate anus, or a deformed ear canal were excluded. Ear temperature measured using calibrated LighTouch Pedi-Q infrared thermometer (core mode). Calibrated before the study began. Rectal temperature measured using Filac digital thermometer. Fever defined as a rectal temp. of 38.0 °C or greater.	1,175 pairs of rectal and ear temperature measurements were obtained. The mean rectal temperature was 37.58ºC (SD = 0.68) the mean ear temperature was 37.60ºC (SD = 0.85). The correlation coefficient for the two measurements was 0.64 (*P*< 0.0001). No difference by age.
Petersen-Smith[81] <u>Study type:</u> Prospective cohort study EL: III	Population size: 235 Inclusion/exclusion: Age 0–36 mths. 55.6% boys. 2 general paediatric practices. Children having obviously abnormal otic or rectal structures were excluded. Tympanic temperature measured using First Temp. genius 3000A (Rectal mode). Calibrated. Rectal temperature measured using glass mercury thermometer. Calibrated. Placement time 3 minutes.	R squared = 0.23; 95 °CI for the slope = 0.34 to 0.55. 62% of measurements were divergent by at least 0.3ºC, 35% by greater than 0.6ºC. Details of data collection were not given (blinding, number of investigators, transcription of results).

Citation/EL	Method	Results
Sehgal[82] <u>Study type:</u> Prospective cohort study EL: III	60 febrile paediatric patients attending emergency departments. 31 boys 29 girls. Age 0.67 mths to 9 years (mean 4.47 years). Children < 6mths, otoscopically diagnosed cases of suppurative otitis media, otitis externa and those with moderate to large amounts of wax. Those with CSF leaks and fissures and those receiving enemas were excluded. Tympanic temperature measured using Thermoscan Instant thermometer IRT 1020. An offset (0.42 °C) preset by the manufacturer was used. Rectal temperature obtained using a digital thermometer with probe inserted 2 cm into the rectum.	The mean rectal temperature was 38.88ºC (SD = 0.86). Two readings from each ear were recorded and the average taken. Mean in the right ear was 39.0ºC (SD = 0.89). Mean in left ear was 38.97ºC (SD = −0.92). Because the correlation between readings of the two ears was high (r = 0.992, P< 0.01) the mean of the two values was taken for further analysis (38.98ºC (SD = −0.9). The rectal temperatures were significantly correlated with mean ear temperature (r = 0.994, P< 0.01). The mean temperature difference between mean ear and rectal was 0.1ºC (SD = 0.04).

Review question 3

How accurate are the readings of temperature from different sites of the body in young children and how do these sites compare in the ability to detect fever?

Citation/EL	Methods	Results
Banco[86] Study type: Prospective cohort study EL II	Perceived fever vs. RT(< 4yr) or OT(> 4 years) by either mercury or digital thermometer according to the nurses' preference. Fever: OT ≥37.8 °C or RT ≥38.3 °C.	8.9% (27/303) children had temp. taken at home. 86.1%(216/303) mums believed that they can estimate the presence/absence of fever. 5.0% (15/303) mums believed that they cannot estimate the presence/absence of fever. Sites of palpation (n = 303): forehead (54.5%), face (17.2%), abdomen and torso (8.2%), neck (2.0%) and arms (1.0%), observation (0.3%), child told mum when he had fever (2.0%)□ subtotal = 261 (86.1%). Have no method: n = 15; use thermometers: n = 27. 17.6% (46/261) had fever. 52.3% (34/65) believed their children had fever were proved to be correct. Overall, the palpation has 52.3% PPV, 93.9% NPV, sensitivity 73.9% and specificity 85.6%. Palpation of the trunk and abdomen has 71.4% PPV; but SMLL number (n = 25). Subgroup: < 2yr. Palpation has sensitivity of 90% to identify RT ≥38.9 °. Only recruited those who were accompanied by their mothers. The impact of excluding other caregivers is not clear. Blind design.
Hooker[87] Study type: Prospective cohort study EL II	Population size: 180 children. Inclusion/exclusion: Age: 2days to 48 months. Mean age 14.6±11.8 months. Perceived fever vs. tympanic temp. (TT) measured by non-contact tympanic thermometer (3 times rectal-equivalent mode + 3 times actual-ear mode) vs. RT by mercury thermometer.	55%(99/180) children had fever as determined by RT. Parental palpation to detect fever had : 81.8% sensitivity and 76.5% specificity. The parental perception and RT agreed 79% of the time (95% CI :73–85%). The first dreading of TT in rectal-equivalent mode had sensitivity of 74.7%, specificity of 96.3% to detect fever. This method agreed with 84% of the time (95% CI :78–89%). The maximum of 3 consecutive TT had sensitivity of 78.8%, specificity of 96.3% to detect fever. This method agreed with 87% of the time (CI not reported).

Citation/EL	Methods	Results
		Fever: RT ≥38.0 °C or TT ≥38.0 °C by rectal-equivalent mode; TT ≥37.7 °C by actual-ear mode. Convenient sampling. The tympanic thermometers and calibrating instruments were provided by the Thermoscan Inc.
Nwanyanwu[88] Study type: Prospective cohort study EL II	Population size: 1120 Malawian children. Inclusion/exclusion: Age: children < 5yr, mean18 months. All children were palpated by the mums, and all but 2 by clinical officers. Perceived fever/no fever vs. RT ≥38.0 °C by mercury thermometer.	36.7% (410/1120) had true fever. Among the 147 children judged to afebrile by mums, 11 (7.5%) were false negative. Of 553 judged to afebrile by clinical officers, 73 (13.2%) were false negative. Of the 410 children with true fever, clinical officers and mums incorrectly considered 73 (17.8%) and 11 (2.6%) to be afebrile, respectively. Of the 973 judged to be febrile by mums, 574 (59.0%) were found to be afebrile (false positive). Of the 565 judged to be febrile by clinical officers, 228 (40.4%) were found to be afebrile (false positive). Mums were more likely to report false positives (*P*< 0.001). Mums had sensitivity of 97.3%; specificity: 19.2%. NPV:92.5%, PPV:41.0% Clinical officers had sensitivity of 82.2%; specificity: 67.8%, NNP: 87.0%, PPV: 59.6%. Authors concluded that palpation is not a reliable method to determine fever. All children were palpated by the mums, but 2 by clinical officers. Funding source: US Agency for International Development.
Singhi[89] Study type: Prospective cohort study EL II	Population size: 301 mothers and their children. Inclusion/exclusion: Children between 3 months to 12 years, who were brought to the paediatric OPD or A&E between 9am to 1pm. Perceived fever vs. axillary temp. (< 5yr) was taken with mercury thermometer, orally > 5 years.	The definition of fever was AT > 37.4 °C. The mothers were requested to demonstrate the methods they used for assessment of fever without a thermometer and to record their estimates of low, high or very high. No report on the definition of fever for those who made temp. taken orally. The choice of statistical analyses.
Ernst[90]	Population size: 100 parents of acutely ill children Inclusion/exclusion: Acutely ill children (age 1 months to 18 years) who had admitted to using palpation as their	80% (80/100) of parents were able to detect fever or no fever by touching (sites of palpation not reported). 36/52 (73.0%) correctly reported fever with predictive value of 69.2%, sensitivity: 90.0%. 44/60 (73.3%) afebrile children were correctly identified with specificity of 73.3%.

Citation/EL	Methods	Results
Study type: Prospective cohort study EL II	sole method of temp. measurement. Fever or no fever by parental palpation vs. RT ≥38.3 °C or OT ≥37.7 °C measured by digital thermometer (IVAC model No. 811A).	For children < 2 years, 88.3% (53/60) parents correctly detected the presence and absence of fever. 83.9% (26/31) report of fever was correct with predictive value of 83.9% (? No enough info to calculate PPV, this figure could be sensitivity). 28 children < 2 years and had fever, 26 were correctly identified (sensitivity 92.8%). Of the 32 children < 2y without fever, 26 were correctly identified (specificity: 84.4%). Acute illness not defined. Sites of palpation not reported. Number of children < 2yr is small, be cautious to draw conclusion. Provided information is not sufficient to check the calculation.
Bezerra Alves[91] Study type: Prospective cohort study EL III	Population size: A convenient sample of 169 children. Inclusion/exclusion: Children presenting to hospital though to have been febrile were recruited. Aged between 2 months to 13 years (mean:32, SD: 21 months). Children who were too ill (not defined) were excluded. Definition of fever: AT ≥38.0 °. Perceived fever (touch children's neck) vs. AT measured by mercury thermometer (judging from the context, not stated explicitly).	Of 169 children, 137 (81.1%) were febrile. In 104 (75.9%) the maternal determinations of fever by palpation were correct. In another 32 children without fever, mothers identified 29 (90.6%) children as non-febrile. The positive predictive value was 97.2% (95% CI 91.4–99.3%) and the negative predictive value was 46.8% (95% CI 34.2–59.8%). Sensitivity : 75.9% (95% CI 67.7–82.6), specificity 90.6% (95% CI 73.8–97.5). Number and criterion of exclusion were not reported, may subject to bias. Site of palpation not reported.
Morley[59] EL:II	In a Zambian hospital, medical students and the child's mother felt children's abdomen, forehead, and neck and independently recorded whether the child felt hot. Simultaneously, a mercury thermometer was used to measure axillary temperature for exactly 3 minutes. Rectal temperature measurement was not	In total, 1090 children aged 1 month to 16 years (median 2 years) were studied. The mean ambient temperature was 24.5 (SD 2.0)°C; the mean axillary temperature from 24 children not recently vaccinated and with no complaint was 36.7 (2SD 1.12)°C. Therefore 37.8 °C or higher was defined as a fever. With this definition, 236 (27%) children had fever. The mothers assessed 862 children and thought 574 (67%) were warm or hot. Their sensitivity was 94% (221/236), specificity 44% (273/626),PPV 39% (221/574), NPV 95% (273/288) and RR 7.8. Two students assessed 1086 children and thought 525 (48%) were warm or hot. Their sensitivity was 94% (257/274), specificity 67% (544/812), PPV 49% (257/525), NPV 97% (544/561) and RR 16.33. Two students, working

Citation/EL	Methods	Results
	permitted at this hospital.	independently, had remarkably similar results (sensitivities 95% and 94%, PPV 50% and 47%).

Review question 5

Can the height of body temperature in a young child with fever be used to predict the risk of serious illness* or mortality?

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr>
<td>Hewson[93]

study type:
prospective cohort study
EL:2+</td>
<td>Country:
Australia
Aim:
To perform a multicentre follow-up study to determine if previously identified markers of serious illness in early infancy were robust and statistically reliable.
Setting, inclusion/exclusion:
This study was conducted from July 1991 to June 1992. This was a study on the clinical marks of serious illness in young infants aged 1-to 26 weeks presenting to the Emergency Departments of Royal Children’s Hospital and two general Melbourne metropolitan Hospitals for 12 months.
Rectal temperature was used in this study. Type of thermometer is not specified. The predictive values of temp. < 36.4 °C, > 38.0 °C and > 38.9 °C were explored. Exclusion criteria were not reported
Clinical markers:
1. Drowsiness
(a) occasional
(b) frequent
(c) on examination
(d) any (history or on exam)
2. Decreased activity
3. (a) difficult breathing
(b) moderate – severe chest wall</td>
<td>From 3806 assessments (mean age: 77 days. 62.4% were < 13 weeks) there were 312 infants assessed as being seriously ill (8.2%).
Table :The diagnostic values of the markers of serious illness for all infants from 0–26 weeks.
<table>
<tr><th></th><th>No</th><th>PPV (%)</th><th>NPV (%)</th><th>Relative risk</th><th>Sensitivity (%)</th><th>Specificity (%)</th></tr>
<tr><td>Temp.
(a) 38.1–38.9 °C
(b) > 38.9or < 36.4 °C
(c) > 38.1 or < 36.4 °C</td><td>
252
101
353</td><td>
29.0
41.6
32.6</td><td>
92.2
91.7
93.0</td><td>
3.62
5.13
4.71</td><td>
17.5
10.1
27.6</td><td>
95.8
98.6
94.4</td></tr>
</table>
Table :The cumulative diagnostic values of the markers of serious illness*.
<table>
<tr><th></th><th>Cumulative Sensitivity (%)</th><th>Specificity (%)</th><th>PPV (%)</th><th>NPV (%)</th><th>Relative risk</th></tr>
<tr><td>Temp. > 38.1 or < 36.4 °C</td><td>62.2</td><td>76.8</td><td>18.9</td><td>95.5</td><td>4.2</td></tr>
</table>
 excluding infants with inguinal hernia.

Data collection was not blind, randomised and didn’t report the measurements of reference standard before and after intervention. Control Group: not reported. No details of follow-up although this study was claimed as multicentre follow-up study. The sensitivity, specificity, positive predictive value and negative predictive value were used for statistical analysis but 95% CI did not report. The risk of bias on this study was likely to affect the result although the study related to infant with fever.</td>
</tr>
</table>

Citation/EL	Method	Results
	recession 4. (a) pale on history (b) pallor on exam 5. (a) feeding 2/3–1/2 (b) feeding < 1/2 6. Urine output 7. Vomits: > 5/24 hr 8. Convulsion 9. Bile-stained vomiting 10. Respiratory grunt 11. Lump > 2 cm 12. Temp. (RT, type of thermometer not reported) (a) 38.1–38.9 °C (b) > 38.9or < 36.4 °C (c) > 38.1 or < 36.4 °C <u>Definition of serious illness:</u> Either having a serious investigation result (i.e. positive pathological bacterial culture from blood, urine, CSF, faeces, or a chest-x ray reported as showing consolidation in a febrile patient) or by requiring significant treatment in hospital as supervised by independent staff (i.e. NG or IV fluid, parental antibiotics, O2 > 30% or surgery).	
Pantell[120]	<u>Country</u>: District of Columbia, and Puerto Rico. <u>Aim:</u> To characterize the management and	They included 3066 infants≤3 months (mean:7.0 wk, SD:3.4 wk). Bacteraemia was detected in 1.8% of infants (2.4% of those tested) and bacterial meningitis in 0.5%. Well-appearing infants aged 25 days or older with fever of less than 38.6 degrees C had a rate of 0.4% for bacteraemia/bacterial meningitis. Frequency of other illnesses included urinary tract infection, 5.4%; otitis media, 12.2%; upper respiratory tract infection, 25.6%; bronchiolitis, 7.8%; and gastroenteritis, 7.2%.

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td>study type:
prospective cohort study
EL:2+</td><td>clinical outcomes of fever in infants, develop a clinical prediction model for the identification of bacteraemia/bacterial meningitis, and compare the accuracy of various strategies.
Setting, inclusion/exclusion:
From February 28, 1995, through April 25, 1998, offices of 573 practitioners from the Pediatric Research in Office Settings (PROS) network of the American Academy of Pediatrics in 44 states, Consecutive sample of 3066 infants aged 3 months or younger with temperatures of at least 38 °C seen by PROS practitioners with no major co-morbidities (e.g. congenital anomalies, extreme prematurity, conditions associated with organ system failure).
Temperature was determined by the maximum rectal temp. taken in office or reported by parents, or add 0.5 °C to axillary temp. Mean : 38.7, SD: 0.5 °C.
The factors of guideline model:
• Age (day)*
≤ 30
31–60
• Appearance
Well
inattentive
No smile
Decrease social interaction</td><td>Table :Multivariate predictors of bacteraemia/bacterial meningitis before lab test (n = 3066)
<table><tr><th>Factor</th><th>No.</th><th>UOR</th><th>AOR (95% CI)</th><th>P</th></tr><tr><td>Age (day)*
≤ 30
31–60</td><td>
775
1220</td><td>
5.72
2.55</td><td>
5.56 (2.50–12.4)
3.03 (1.35–6.81)</td><td>
< 0.001
0.007</td></tr><tr><td>Temp. (°C)**
38.5–38.9
39.0–39.4
≥ 39.5</td><td>
1049
458
198</td><td>
2.63
2.59
4.51</td><td>
2.37 (1.22–4.63)
1.84 (0.84–4.37)
3.61 (1.40–9.25)</td><td>
0.01
0.12
0.008</td></tr><tr><td>Abnormal cry</td><td>251</td><td>5.16</td><td>2.23 (1.16–4.29)</td><td>0.02</td></tr></table>*: baseline: age > 60 days.
**: baseline: well or minimally ill
***: baseline: temp. < 38.5 °C.
Table :Multivariate predictors of bacteraemia including lab test (n = 1746)
<table><tr><th>Factor</th><th>AOR (95% CI)</th><th>P</th></tr><tr><td>Age (day)*
≤ 30
31–60</td><td>
4.03 (1.74–9.37)
2.39 (1.00–5.71)</td><td>
0.001
0.06</td></tr><tr><td>Temp. (°C)**
38.5–38.9
39.0–39.4
≥ 39.5</td><td>
2.03 (1.03–4.02)
1.79 (0.78–4.09)
2.90 (1.09–7.74)</td><td>
0.04
0.17
0.03</td></tr></table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>• Medically insured
• Temp. (°C)**
38.5–38.9
39.0–39.4
≥ 39.5
• Receive care after hours
• Source of fever</td><td>Guideline model has sensitivity: 95.2%, specificity: 35.2% to diagnose bacteraemia.
Three-structured analysis model (clinical assessment, age < 25 d and temp. ≥38.6 °C) has sensitivity: 93.6%, specificity: 27.3% to diagnose bacteraemia.
PROS practitioners' experience: initial treatment with antibiotics has sensitivity: 97.1%, specificity: 35.5% to diagnose bacteraemia.
Not all febrile infants were enrolled during study period, infants eligible but not enrolled were slightly older, suggesting that SBI may be less than reported. The distribution in the sample is likely to be representative of infants in community-based practice but not in emergency department.</td></tr>
<tr><td>Nademi[121]

study type
Prospective cohort study

EL:2+</td><td>Country:
UK.
Aim:
To assess the causes of fever and identify clinical and laboratory features suggesting serious disease in U.K.
Setting, inclusion/exclusion:
This study was conducted in August and October 1999
All patients presenting fever to the paediatric assessment units at Newcastle General Hospital. Children presenting to hospital with temperatures ≥38 °C were included and patients with a temp. < 38 °C were excluded.
Definition of serious illness: sepsis, meningitis, toxic shock syndrome, brain abscess, pneumonia, UTI, ischiorectal abscess, appendicitis.
Twenty two (16%) had already received antibiotics (usually Amoxicillin) within last</td><td>One hundred and forty one children between 8 days and 16 years of age (mean age 3.3 years) were studied, 64% male, 55% aged under 2 years. Serious disease was present in 41 (29%) with 31 (22%) microbiologically or radiologically proven and the other 10 given a diagnosis of sepsis cause including three patients with clinical signs of meningococcal disease but without any positive culture.
35/41 (86%) of patients with serious bacterial infections had temperatures between 38 and 39 °C and 3 (7%) had temperature between 38–39 °C. Ninety six percent were casualty or GP referrals and 4% were tertiary referrals. Twenty nine percent (41/141) had serious disease but microbiologically or radiologically proven in only 22% (31/141); pneumonia (nine), meningitis (seven), sepsis (five), urinary tract infection (five), brain abscess (two), toxic shock syndrome (one), appendicitis (one), ischiorectal abscess (one). Forty two percent (5/12) of microbiologically proven meningitis and sepsis and 36% (8/22) of all meningitis and sepsis were meningococcal. 71% had non-serious diseases.
Table :Comparison of sensitivity, specificity, PPV and NPV of all variables with 95% CI to detect serious illness (n = 41)
<table>
<tr><th></th><th>Sensitivity %</th><th>Specificity %</th><th>PPV %</th><th>NPV %</th><th>Relative risk</th></tr>
<tr><td>T> 39 °C.</td><td>14 (3–25)</td><td>82 (74–89)</td><td>25 (7–42)</td><td>70 (61–78)</td><td>0.83</td></tr>
<tr><td>T> 39.5 °C.</td><td>7 (0–15)</td><td>93 (87–98)</td><td>30 (1–58)</td><td>71 (63–78)</td><td>1.03</td></tr>
</table></td></tr>
</table>

Citation/EL	Method	Results
	24 h, including 8 serious illness. Axillary temperature was measured routinely in children < 3yr; tympanic temperature in children > 3yr. Type of thermometer not specified.	
Teach[122] study type: prospective cohort study EL:2+	Country: USA Aim: To determine the relationship between the duration of fever as reported by caregivers and the likelihood of occult bacteraemia in highly febrile (≥39.0 °C) children. Setting, inclusion/exclusion: A prospective cohort study performed November 1during May 1987to 1991as part of a prior, multicenter, randomized, interventional trial of oral versus intramuscular antibiotics in the prevention of complications of occult bacteraemia in febrile children presenting to nine urban paediatric emergency departments at eight medical centers. The outcome measure was the presence of bacteraemia. Participants included children three to 36 months of age with a temperature of ≥ 39.0 degrees C and a nonfocal illness (or uncomplicated otitis media) managed as outpatients. Exclusions were toxic clinical appearance,	Of the 6680 randomized patients (range 3–36 months. Descriptive statistics on age not reported), 6619 (99.1%) had a culture of their blood and a valid reported duration of fever. The mean initial temperature was 39.8±0.56 °C. Mean tem for patients occult bacteraemia (40.0±0.61 °C) was significantly higher (*P*< 0.001) than those without (39.8±0.55 °C). The duration of fever of both groups ranged from < 1 to 14 days. 6498 patients (98.2%) had a duration of fever of < 5 days. The mean rank of duration of fever of patients with bacteraemia was significantly lower than the mean rank of those without bacteraemia (2885 vs. 3323, *P* = 0.009 by Mann-Whitney U test). A significantly greater proportion of patients with fever < 1 day had bacteraemia than patients with fever ≥ 1 days (77/2018 vs. 115/4601, *P* = 0.004 by Chi square test.) A significantly greater proportion of patients with fever < 2 day had bacteraemia than patients with fever ≥ 2 days (158/4893 vs. 34/1726, *P* = 0.009 by Chi square test.) Decision of having cut-off point as fever as BT ≥39.0 °C not justified.

Citation/EL	Method	Results
	a known or suspected allergy to amoxicillin or ceftriaxone, a focal bacterial infection other than otitis media, a specific viral infection (e.g. varicella), a known immunodeficiency or underlying chronic conditions, antibiotic therapy or immunisation in the previous 48 h, and lack of inform consent.	
Crain[95] study type: prospective cohort study EL:2+	Country: USA Aim: To gain info on the incidence of bacteraemia in a group of infants with fever who presented to such in an emergency room. Further, to see if there were any criteria by which house officers at the time of first exam could predict which infants would turn to have bacteraemia. Setting, inclusion/exclusion: This study was conducted in Bronx Municipal Hospital Centre from Oct. 1, 1979 to Sept. 30, 1981 All infants received a full evaluation for sepsis and were admitted for antibiotic therapy pending culture results. Infants with a history of fever at home of ≥ 38.0 °C, regardless of their temp. in the emergency room were recruited . Assessments included impression on tone, colour, activity, cry and irritability. An overall impression of the likelihood that the infant had sepsis was a global judgement,	They recruited 175 infants 8 weeks or younger. Culture-positive infections occurred in 6.3% (n = 11); the incidence of bacteraemia was 3.4% (n = 6). Of the 175 infants, group A with 41 (23.4%) infants had source of fever identified prior to lumbar puncture (broncholitis:2; breast abscess:1; UTI:1; otitis media: 24; pneumonia: 11; DPT reaction: 2). Group B of 42 (24%) infants, a source of infection was identified, until some time after lumbar puncture (meningitis: 2; osteomyelitis: 1; gastroenteritis: 9; aseptic meningitis: 26; URI:4). Group C contained 92 (52.6%) infants who had no identifiable source of fever at any time (including non-specific viral syndrome). In total, 11 infants (6.2%) had positive bacteria culture, and six (3.4%) had bacteraemia, no infant with pneumonia had a positive blood culture, and neither infants with bacterial meningitis had another identified soft-tissue focus of infection. Mean temp. was 38.8 °C; five (3%) infants had temp. > 39.8 °C. Exact probability tests (details not provided) to assess the relationships between variables and bacteraemia. The following variables are not significantly associated with bacteraemia: WBC ≥15000/mm^3, and count ≥500/mm^3, temp. ≥38.6 °C (the median), impression of irritability, tone, cry, or activity level during exam (*P* values not given). An ESR was obtained at the time of presentation in 99 of 134 infants without an identified fever source. Four of five infants with bacteraemia had an ESR ≥ 30, compared with only six of the 94 without bacteraemia. The relationship between ESR and bacteraemia as significant (*P*< 0.001), but use of ESR alone would have cause them to miss one instance (1/6: 16.67%) of bacteraemia. Impression of sepsis during the first exam was significantly associated with bacteraemia. The impression was either strong or ambivalent for all five of the infants with bacteraemia compared with 54 (42%) of other 129 infants (*P*< 0.02).

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>which a subsequent sample of 28 (51%) of the house staff indicated was based primarily on 5 factors: the infants' level of activity (mentioned by 79%), feeding pattern (79%), irritability (82%), responsiveness (89%) and ability to be consoled (100%).

Lab test:

CBC, blood culture, serum glucose, lumbar puncture for cell count, chemical analysis and culture, urine analysis (by suprapubic aspiration). CRX, stool culture, ESR, WBC.</td><td></td></tr>
<tr><td>Weber[98]

<u>study type:</u>

prospective cohort study

EL: 2+</td><td><u>Country:</u>

Ethiopia, the Gambia. Papua New Guinea and the Philippines.

<u>Aim:</u>

To identify simple procedures for identifying infants with infection that need referral for treatment are therefore of major public health importance.

<u>Setting, inclusion/exclusion:</u>

At hospitals or outpatient clinics where large number of sick infants were seen from April 1978 to March 1979.

Rectal temperature for children < 5; oral temperature for > 5 years. Type of thermometer not reported.

At each study site, infants < 91 days of age seen consecutively for acute care with chief complaints indicating possible</td><td>They recruited 3303 infants < 2 mo.

Level 0: No abnormality, n = 2585 (78.3%); level 1: Mild hypoxemia (90%≤SaO2< 95%) or radiologic pneumonia; n = 346 (10.5%); and level 2: Severe hypoxemia (SaO2< 90%) or bacteraemia or meningitis: n = 372 (11.3%); and 194 (5.9%) died. There were 120 cases of sepsis, 34 of meningitis and 259 of hypoxemia.

Table : Independently significant predictors of Ordinal Outcome 1 or 2vs 0 in the three groups of general status, respiratory signs and meningitis signs, for the age group 0–6 days.

<table>
<tr><th>Signs or symptom</th><th>Prevalence (%)</th></tr>
<tr><td>General status</td><td></td></tr>
<tr><td>Feeding ability reduced</td><td>17*</td></tr>
<tr><td>No spontaneous movement</td><td>11*</td></tr>
<tr><td>Temp. > 38 °C</td><td>19*</td></tr>
<tr><td>Drowsy</td><td>7</td></tr>
<tr><td>History of feeding problem</td><td>16</td></tr>
<tr><td>History of change in activity</td><td>21</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr>
<td></td>
<td>infection were eligible. This report only analyse the age group 0–59 days. Entry criteria were intended to include a wide spectrum of illness severity and to ensure that virtually all infants with serious infection would be included.

Children with congenital heart disease and hypoxemia were excluded.

All infants underwent a standardized history and physical exam to assess the degree of signs and symptoms. All had and pulse oximetry. Infants with pre-specified symptoms associated with bacterial infection had lab evaluation that included blood culture, WBC, CXR (n = 1809). Specific criteria were used to identify infants for lumbar puncture (n = 401).

Definition of sepsis:

The growth of an unknown pathogen in cultures of blood.

<u>Ranking of disease severity:</u>

Level 0: No abnormality

Level 1: Mild hypoxemia (90%≤SaO_2< 95%) or radiologic pneumonia.

Level 2: Severe hypoxemia (SaO_2< 90%) or bacteraemia or meningitis.

Death was separately analysed.</td>
<td>
<table>
<tr><td>□ Agitated</td><td>4</td></tr>
<tr><td>□ Digital capillary refill</td><td>11*</td></tr>
<tr><td>Respiratory signs</td><td></td></tr>
<tr><td>□ Lower chest wall indrawing</td><td>14*</td></tr>
<tr><td>□ Respirator rate > 6</td><td>23*</td></tr>
<tr><td>□ Grunting</td><td>2*</td></tr>
<tr><td>□ Cyanosis</td><td>4*</td></tr>
<tr><td>Meningitis signs</td><td></td></tr>
<tr><td>□ History of convulsion</td><td>4*</td></tr>
<tr><td>□ Bulging fontanel</td><td>2</td></tr>
</table>
*: these signs comprise a restricted group that were considered for a more specific diagnostic algorithm, (see next table)

Table :Sensitivity, specificity and negative likelihood ratio of different combination rules for predicting severe illness by ordinal outcome scale (0 vs. 1+2)
<table>
<tr><td></td><td colspan="2">0–59 days</td><td colspan="2">0–6 days</td><td colspan="2">7–59 days</td></tr>
<tr><td rowspan="2">Fever (temp.> 38 °C) and any other sign</td><td>Sn 25</td><td>LR+2.78</td><td>Sn 21</td><td>LR+1.31</td><td>Sn 26</td><td>LR+3.25</td></tr>
<tr><td>Sp 91</td><td>LR- 0.82</td><td>Sp 84</td><td>LR- 0.94</td><td>Sp 92</td><td>LR- 0.80</td></tr>
</table>
*: Sn: sensitivity, Sp: specificity, LR+: positive likelihood ration; LR-: negative likelihood ratio.

Table :Association of clinical signs with sepsis, meningitis, hypoxemia and death. OR adjusted for place of study, weight and age.
<table>
<tr><td></td><td></td><td colspan="2">Sepsis</td><td colspan="2">Meningitis</td></tr>
<tr><td></td><td>Prevalence</td><td>OR</td><td>95% CI</td><td>OR</td><td>95% CI</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td>(%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Temp. < 35.5</td><td>2</td><td>3.7</td><td>1.8–7.3</td><td>4.2</td><td>0.8–22.5</td></tr>
<tr><td>Temp.≥ 38</td><td>17</td><td>3.6</td><td>2.6–5.1</td><td>11.8</td><td>5.7–24.6</td></tr>
<tr><td></td><td></td><td colspan="2">Hypoxemia</td><td colspan="2">Death</td></tr>
<tr><td></td><td>Prevalence (%)</td><td>OR</td><td>95% CI</td><td>OR</td><td>95% CI</td></tr>
<tr><td>Temp. < 35.5</td><td>15</td><td>2.0</td><td>0.9–4.2</td><td>2.1</td><td>0.9–4.8</td></tr>
<tr><td>Temp.≥ 38</td><td>22</td><td>1.0</td><td>0.5–1.9</td><td>1.1</td><td>0.5–2.2</td></tr>
</table>
Table :Association of clinical signs with the age group 7–60 days. OR adjusted for the place of study and weight.
<table>
<tr><td></td><td colspan="5">Age group 7–60 days</td></tr>
<tr><td></td><td></td><td colspan="2">Outcome: level 1 or 2 (cf.0)</td><td colspan="2">Outcome: level 2 (cf.0 or 1)</td></tr>
<tr><td></td><td>Prevalence (%)</td><td>OR</td><td>95% CI</td><td>OR</td><td>95% CI</td></tr>
<tr><td>Temp. < 35.5</td><td>2</td><td>2.4</td><td>1.2–4.7</td><td>3.4</td><td>1.7–6.8</td></tr>
<tr><td>Temp.≥ 38</td><td>15</td><td>2.7</td><td>2.2–3.4</td><td>3.4-</td><td>2.6–4.5</td></tr>
</table>
</td></tr>
<tr><td>Haddon[123]

<u>study type :</u>
prospective cohort study</td><td><u>Country:</u>
Australia
<u>Aim:</u>
To determine the prevalence of bacteraemia in febrile children aged 3 to 36 months presenting to a paediatric</td><td>They recruited 534 (mean age 16.4 months, SD 7.9 months)300 male, 234 female)children; 50% of eligible children. 18/534 (3.4%, 95% CI 2.0 to 5.3) with bacteraemia (S. pneumoniae, n = 15; N. meningitidis, n = 2; Klebsiella pneumoniae, n = 1); 12 male, 6 female.

11/18 had no focal signs of infection; 7/18 had signs or symptoms of upper respiratory tract infection (n = 4) or otitis media (n = 3)
6/18 were admitted to hospital (for febrile convulsions, n = 2; for suspected UTI, n = 1; for WCC ≥20x10^9/L, n = 3).</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td>E: 2+</td><td>emergency department
<u>Setting, inclusion/exclusion:</u>
Children presenting between May 1996 and May 1997 at the emergency room in the Royal Children’s Hospital with a temperature ≥39 °C (tympanic). 125 children on antibiotics in week before presentation at ER; none had positive blood cultures. Excluded only with varicella, croup or herpes gingivostomatitis
Fever was defined as tympanic temperature ≥39 °C, regardless of source
Demographic and clinical details taken; general condition assessed on McCarthy Observation Scale, where score ≤10 is associated with low risk of serious illness; and likelihood of bacteraemia predicted by medical staff (1–2 = unlikely; 3 = unsure; 4–5 = likely). Full blood count and culture taken and final diagnosis of illness determined by one investigator
Bacteraemia diagnosed if blood culture showed growth of a pathogenic organism.</td><td>Final diagnosis of 18 children serious illness :Bacteraemia, n = 12, Otitis media, n = 3, Periorbital cellulitis, n = 1, UTI, n = 1, Pneumonia, n = 1
Table :Comparison with children without bacteraemia, mean (SD)
<table>
<tr><th></th><th>Bacteraemia (n = 18)</th><th>No bacteraemia (n = 516)</th><th>P value</th></tr>
<tr><td>Age (months)</td><td>17.6 (9.4)</td><td>16.4 (7.9)</td><td>0.56</td></tr>
<tr><td>Fever (°C)</td><td>39.7 (0.39)</td><td>39.7 (0.55)</td><td>0.91</td></tr>
</table>
Children with fever of 12 hours or less duration were more likely to have bacteraemia than those who had fever longer (10/103 v. 8/411; RR 4.6, 95% CI 1.8 to 12, P< 0.001); predictive accuracy of fever < 12hrs for occult bacteraemia was 9.4% (95% CI 4.8 to 16).</td></tr>
<tr><td>Hsiao[126]
<u>Study type:</u>
Prospective cohort study.
EL 2+</td><td><u>Country:</u>
USA
<u>Aim:</u>
To investigate the aetiology of fever and usefulness of screening tests in older (2–</td><td>Serious bacterial illness (SBI) was diagnosed in 44 (10.3%) of 429 infants: 41 with bacteriuria and 4 with bacteraemia (1 infant had concurrent Escherichia coli bacteriuria and bacteraemia). Lumbar puncture, performed in 58 (13.5%) infants, revealed no cases of bacterial meningitis. DFAs were positive in 163 (38.0%) infants: the majority were RSV or influenza A. SBI was noted in 4.9% of infants with positive DFA. Height of fever were not significant predictors of SBI (38.4±1.0 vs. 38.5±0.8; P = 0.18). Duration of fever was longer in infants with SBIs (18.6±21.7 hr) than those without (26.5±41.5hr) (P< 0.01). White blood cell count (17.1 K/mm3 vs. 12.4 K/mm3) and CRP (2.6 mg/dL vs. 0.9 mg/dL) were elevated in infants with SBI, as was the Yale Observation Score (9.4 vs.</td></tr>
</table>

Citation/EL	Method	Results
	6 months) infants. Method: It's a prospective study of febrile infants 57–180 days old. Evaluation included blood and urine tests and direct fluorescent antibody (DFA) of nasal swabs for respiratory viruses. Additional studies were performed at the discretion of managing clinicians.	8.0).
Ronfani[99] study type: prospective cohort study EL: 2+	Country: Brazil Aim: To estimate sensitivity, specificity, and predictive value of different signs of severe bacterial infection (SBI) in neonates upon presentation to an emergency and neonatology department Setting, inclusion/exclusion : All neonates (< 28 days) presenting at hospital and admitted to the emergency and neonatology department of Instituto Materno Infantil de Pernambuco from1 March 1995 to 29 Feb 1996 infants with 'birth-related problems' were excluded. Number not reported. Data on age, sex, type of delivery, birthweight, gestational age, weight and length at admission, type of feeding collected at admission Signs reported by mother/carer: • Difficult breathing • Fever	They recruited 83 (42 male, 39 female) in total. SBI = 41 (49.4%); probable SBI = 9 (10.8%); other disease = 33 (39.8%) Most common diagnosis: Among SBI: • pneumonia, n = 22 • sepsis, n = 10 • meningitis, n = 4 • conjunctivitis, n = 4 Among other diseases: • jaundice, n = 9 • mild diarrhoea, n = 6 • convulsions, n = 4 Signs most frequently reported by mother/carer: • Difficult breathing, 32% • Diarrhoea, 26% • Fever, 19% • Cough, 19% • Vomiting, 19% • Jaundice, 16% • Cyanosis, 14%

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>
• Diarrhoea
• Cough
• Vomiting
• Duration of all the above

Signs reported by doctor:

• severe chest indrawing
• Fast breathing
• Not looking well

Lab:

• Complete blood count
• CRP
• Blood culture
• Chest x-ray, CSF microscopy and culture, and urine culture only when CNS infections and UTI were suspected

<u>Designation of infection status by doctor at discharge (reference standard):</u>

• SBI, included sepsis, meningitis, severe diarrhoea, lower respiratory tract infection, UTI, severe omphalitis
• Probable SBI
• Other disease
</td><td>
• Not feeding well, 11%

Signs most frequently observed by doctor:

• Severe chest indrawing, 46%
• Fast breathing (60+ breaths/minute), 40%
• Jaundice, 29%
• ‘Not looking well’, 25%
• pallor, 23%
• hypotonia, 22%
• cyanosis, 19%
• dehydration, 18%

Table :Sensitivity, specificity and predictive values of best performing signs for SBI
<table>
<tr><td></td><td>PPV (%)*</td><td>Sensitivity (%)</td><td>Specificity (%)</td></tr>
<tr><td>By mothers</td><td></td><td></td><td></td></tr>
<tr><td>Difficult breathing</td><td>78</td><td>42</td><td>82</td></tr>
<tr><td>Fever</td><td>100</td><td>33</td><td>100</td></tr>
<tr><td>By doctors</td><td></td><td></td><td></td></tr>
<tr><td>S. chest indrawing</td><td>76</td><td>58</td><td>73</td></tr>
<tr><td>Fast breathing</td><td>79</td><td>52</td><td>78</td></tr>
<tr><td>Not looking well</td><td>95</td><td>40</td><td>97</td></tr>
</table>
**No negative predictive value was reported.*

Fever and ‘not looking well’ were the only two signs independently associated with SBI:

Fever RR = 6.47, 95% CI 2.07 to 20.23, *P*< 0.001

Not looking well RR = 7.17, 95% CI 2.44 to 21.02, *P*< 0.001
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td></td><td>
Best sensitivity (74%) found with signs in parallel:
Doctor observed severe chest indrawing or fast breathing or ‘not looking well’ (specificity 67%, PPV 77%)

6 deaths: 4 from SBI group (2 sepsis, 1 pneumonia, 1 meningitis), and 2 from ‘other disease’ group (1 severe rhesus isoimmune haemolytic disease, 1 adrenogenital syndrome)

Table :Sensitivity, specificity and predictive values of best performing signs for pneumonia
<table>
<tr><td></td><td>PPV (%)*</td><td>Sensitivity (%)</td><td>Specificity (%)</td></tr>
<tr><td>By mothers</td><td></td><td></td><td></td></tr>
<tr><td>Difficult breathing</td><td>63</td><td>77</td><td>84</td></tr>
<tr><td>Cough</td><td>88</td><td>64</td><td>97</td></tr>
<tr><td>Fever</td><td>56</td><td>43</td><td>89</td></tr>
<tr><td>By doctors</td><td></td><td></td><td></td></tr>
<tr><td>S. chest indrawing</td><td>45</td><td>77</td><td>66</td></tr>
<tr><td>Fast breathing</td><td>39</td><td>59</td><td>67</td></tr>
<tr><td>Not looking well</td><td>29</td><td>27</td><td>75</td></tr>
</table>
*No negative predictive value was reported.
</td></tr>
<tr><td>Teele[124]

Study type:
prospective cohort study

EL:2-</td><td>Country:
USA
Aim:
To identify clinical and lab features associated with bacteraemia.
Setting, inclusion/exclusion:
A prospective study was conducted during January 1973-June 1974, which blood was obtained from culture from febrile</td><td>
They recruited 600 consecutive febrile children (age range:4 wk – 2 years. Descriptive statistics on age not reported.).
Pathogens were identified in the blood of 19 (3.2%) children.
Table: Analyses of feature associated with bacteraemia
<table>
<tr><td></td><td colspan="2">FUO’</td><td colspan="2">Pneumonia</td><td colspan="2">Pharyngitis</td></tr>
<tr><td></td><td>+*</td><td>Total**</td><td>+</td><td>Total</td><td>+</td><td>Total</td></tr>
<tr><td>Age (months)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

Citation/EL	Method	Results
	children, all of whom were seen by 7 houses officers on the Pediatric Service in the Boston City Hospital. During the study period, children seen by 7 participating physicians in the paediatric 'walk-in centre'; and the exclusion criteria were not reported.	

≤6	0	31	2	22	0	37
7–12	1	63	4	29	1	65
13–18	4	44	2	34	1	43
19–24	0	35	1	15	0	21
RT(°C)						
< 38.9	0	44	0	20	0	19
≥38.9	5	129	9	80	1	64

'FUO: Fever Unknown Origin

*: positive culture of blood at initial visit.

**: No of children cultured.

Table: Analyses of feature associated with bacteraemia (continued)

	Otitis media		Other		All	
	+*	Total**	+	Total	+	Total
Age (months)						
≤6	0	37	0	14	2	116
7–12	1	65	0	30	6	213
13–18	1	43	2	27	10	177
19–24	0	21	0	7	1	94
RT(°C)						
< 38.9	0	35	0	23	0	141
≥38.9	2	131	2	55	19	459

Table :Association of bacteraemia in children with RT> 38.9 and elevated WBC (> 15,000)

Diagnosis	RT> 38.9 and elevated WBC

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td colspan="2">Present</td><td colspan="2">Absent</td></tr>
<tr><td></td><td>+ve culture</td><td>Total no cultured</td><td>+ve culture</td><td>Total no cultured</td></tr>
<tr><td>FUO</td><td>5</td><td>39</td><td>0</td><td>134</td></tr>
<tr><td>Pneumonia</td><td>6</td><td>40</td><td>3</td><td>60</td></tr>
<tr><td>Pharyngitis</td><td>1</td><td>16</td><td>0</td><td>67</td></tr>
<tr><td>Otitis media</td><td>2</td><td>61</td><td>0</td><td>105</td></tr>
<tr><td>Miscellaneous</td><td>1</td><td>16</td><td>1</td><td>62</td></tr>
<tr><td>Total</td><td>15*</td><td>172</td><td>4</td><td>428*</td></tr>
</table>
*: P< 0.001

No description about sampling frame and inclusion/exclusion criteria. Old paper, published in 1975.
</td></tr>
<tr><td>Caspe[125]

<u>Study type:</u>
prospective study

EL:2-</td><td><u>Country</u>:
USA
<u>Aim:</u>
To determine whether clinical assessment is adequate to tell from bacterial or non-bacterial infections.
<u>Setting, inclusion/exclusion:</u>
From July 1st , 1974 to December 31st, 1945 in
Bronx-Lebanon Hospital, a 596-bed community hospital provided primary care of a medically underserved community.
All infants < 60 days with RT ≥ 38.0 °C seen in the outpatient department admitted to the hospital. Infant with well document history of fever were included, regardless of tem on the presentation.</td><td>They recruited 305 infants (age range 4 wk – 2 years. Descriptive statistics on age not reported.)

Table :Comparative features of febrile infants < 60 days with and without bacteraemia
<table>
<tr><td></td><td>No of pt</td><td>Mean age (days)</td><td>Mean temp. (°F)</td><td>% infants with WBC ≥15,000</td></tr>
<tr><td>Bacteraemia</td><td>11</td><td>29.1</td><td>102</td><td>45</td></tr>
<tr><td>No bacteraemia</td><td>256</td><td>37</td><td>101</td><td>15</td></tr>
<tr><td>P</td><td></td><td>Ns</td><td>< 0.01</td><td>< 0.05</td></tr>
</table>
The differential white cell count proved not to be helpful in distinguishing bacterial and non bacterial infections (P value not reported).</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>The Lab tests including

CBC, urine analyses, CXR, CSF and cultures of the blood, CSF and urine (obtained by suprapubic aspiration whenever possible.).</td><td></td></tr>
<tr><td>Singhi[127]

<u>Study type:</u>

prospective study

EL 2−</td><td><u>Country:</u>

India

<u>Aim:</u>

To determine the prevalence and causative organisms of bacteraemia and bacterial infections in febrile children and to assess the usefulness of TLC and ANC and m-ESR for the early diagnosis of bacterial infection

<u>Setting, inclusion/exclusion:</u>

From Jan 1989 to Jul 1990, children aged 1 month to 3 years brought to Pediatric Emergency Service for fever.

Included were children with fever ≤3days duration without apparent source or focus, normal chest x-ray and peripheral blood film negative for malaria parasite. Exclusions were neoplastic and immunosuppressive disease, chronic diseases such as nephrotic syndrome, liver disease or heart disease, and those who had received prior antibiotic therapy

Fever was defined as axillary temperature > 38.5 °C or rectal temperature ≥39 °C</td><td>They recruited 100 (55 male, 45 female) children with mean age of 11.7 months, (SD 8.5 months).

10/100 (10%) with bacteraemia (positive blood culture). Staphylococcus aureus, n = 5; Acinetobacter species, n = 2; Salmonella typhi, n = 1; Salmonella typhimurium, n = 1; Klebsiella pneumoniae, n = 1

9/100 (9%) with bacteraemia (serology positive). Staphylococcus aureus, n = 8; Haemophilus influenzae, n = 1

6/100 (6%) with UTI (urine culture positive)

13/100 (13%) with presumed bacterial infection. Pyomeningitis, n = 8; Otitis media, n = 5

62/100 (62%) with non bacterial illness

Comparison of groups:

<table>
<tr><th></th><th>Bacteraemia (culture +)</th><th>Bacteraemia (serology +)</th><th>UTI</th><th>Otitis Media</th><th>Pyo-meningitis</th><th>Nonbacterial illness</th></tr>
<tr><td>TLC (/mm^3)</td><td>10920±5439*</td><td>10587±4516*</td><td>10800±2545*</td><td>9760±4013</td><td>11950±6235*</td><td>7778±2405</td></tr>
<tr><td>ANC (/mm^3)</td><td>6983±4170</td><td>6830±3418</td><td>6735±2077</td><td>5506±3794</td><td>7532±5329</td><td>4340±2035</td></tr>
<tr><td>mESR</td><td>24.0±6.7*</td><td>19.6±11.3*</td><td>13.6±9.4</td><td>7.6±5.5</td><td>21.2±10.3*</td><td>9.0±7.0</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>Venous blood for TLC, DLC, mESR, serology and culture for all children. Urine culture, CSF analysis and culture in all infants younger than 1 year and in older children when indicated

Bacterial infection divided into bacteraemia and UTI

Bacteraemia defined as positive blood culture or positive serology

UTI defined as positive urine culture.</td><td>
<table>
<tr><td>(mm/l h)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Temp. (°C)</td><td>38.8±0.3</td><td>38.7±0.2</td><td>38.8±0.1</td><td>38.8±0.1</td><td>38.7±0.2</td><td>38.8±0.15</td></tr>
</table>
* P< 0.05 when compared with nonbacterial illness group

Sensitivity, specificity, and predictive values of factors for identifying bacterial infections:
<table>
<tr><th></th><th>PPV (%)</th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>NPV (%)</th><th>Relative risk</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>5.56</td></tr>
<tr><td>TLC ≥15000 /mm^3</td><td>100</td><td>26</td><td>100</td><td>82</td><td></td></tr>
<tr><td>mESR ≥25 mm /l h</td><td>86</td><td>63</td><td>97</td><td>90</td><td>8.6</td></tr>
<tr><td>Temp. ≥ 39.0 °C</td><td>66</td><td>32</td><td>95</td><td>82</td><td>3.67</td></tr>
</table>
</td></tr>
</table>

Review question 6

Can the duration of fever in a febrile young child be used to predict the risk of serious illness* or mortality?

<table>
<tr><th>Citation/EI</th><th>Method</th><th>Results</th></tr>
<tr>
<td>Teach[122]

<u>Study type:</u>
prospective cohort study

EL:2+</td>
<td><u>Country:</u>
USA

<u>Aim:</u>
To determine the relationship between the duration of fever as reported by caregivers and the likelihood of occult bacteraemia in highly febrile (≥39.0 °C) children.

<u>Setting, inclusion/exclusion:</u>

A prospective cohort study performed November 1during May 1987to 1991as part of a prior, multicenter, randomized, interventional trial of oral versus intramuscular antibiotics in the prevention of complications of occult bacteraemia in febrile children presenting to nine urban paediatric emergency departments at eight medical centers. The outcome measure was the presence of bacteraemia.

Participants included children three to 36 months of age with a temperature of ≥ 39.0 degrees C and a nonfocal illness (or uncomplicated otitis media) managed as outpatients.

Exclusions were toxic clinical appearance, a known or suspected allergy to amoxicillin or ceftriaxone, a focal bacterial infection other than</td>
<td>Of the 6680 randomized patients (range 3–36 months. Descriptive statistics on age not reported), 6619 (99.1%) had a culture of their blood and a valid reported duration of fever.

The mean initial temperature was 39.8±0.56 °C. Mean tem for patients occult bacteraemia (40.0±0.61 °C) was significantly higher (P< 0.001) than those without (39.8±0.55 °C). The duration of fever of both groups ranged from < 1 to 14 days. 6498 patients (98.2%) had a duration of fever of < 5 days. The mean rank of duration of fever of patients with bacteraemia was significantly lower than the mean rank of those without bacteraemia (2885 vs. 3323, P = 0.009 by Mann-Whitney U test). A significantly greater proportion of patients with fever < 1 day had bacteraemia than patients with fever ≥ 1 days (77/2018 vs. 115/4601, P = 0.004 by Chi square test.)

A significantly greater proportion of patients with fever < 2 day had bacteraemia than patients with fever ≥ 2 days (158/4893 vs. 34/1726, P = 0.009 by Chi square test.)

Table :Duration of fever related to the likelihood of bacteraemia in febrile children 3–36 months old.
<table>
<tr><th>Duration of fever ≥39.0 °C (days)</th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>PPV (%)</th><th>NPV (%)</th><th>Relative risk</th></tr>
<tr><td>< 1</td><td>40.1</td><td>69.8</td><td>3.8</td><td>97.5</td><td>1.52</td></tr>
<tr><td>< 2</td><td>82.3</td><td>26.3</td><td>3.2</td><td>98.0</td><td>1.60</td></tr>
<tr><td>< 3</td><td>92.7</td><td>10.4</td><td>3.0</td><td>98.0</td><td>1.50</td></tr>
</table>
Among patients with bacteraemia, there was no significant association between duration and fever and age (statistics not reported). There was no significant association between duration and fever and causative organisms(statistics not reported).

Decision of having cut-off point as fever as BT ≥39.0 °C not justified.</td>
</tr>
</table>

<table>
<tr><th>Citation/EI</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>otitis media, a specific viral infection (e.g. vericella), a known immunodeficiency or underlying chronic conditions, antibiotic therapy or immunisation in the previous 48 h, and lack of inform consent.</td><td></td></tr>
<tr><td>Haddon[123]

<u>Study type :</u>
prospective cohort study

EL:2+</td><td><u>Country:</u>
Australia

<u>Aim:</u>
To determine the prevalence of bacteraemia in febrile children aged 3 to 36 months presenting to a paediatric emergency department
<u>Setting, inclusion/exclusion:</u>
Children presenting between May 1996 and May 1997 at the emergency room in the Royal Children’s Hospital with a temperature ≥39 °C (tympanic). 125 children on antibiotics in week before presentation at ER; none had positive blood cultures. Excluded only with varicella, croup or herpes gingivostomatitis

Fever was defined as tympanic temperature ≥39 °C, regardless of source</td><td>They recruited 534 (mean age 16.4 months, SD 7.9 months)300 male, 234 female)children; 50% of eligible children. 18/534 (3.4%, 95% CI 2.0 to 5.3) with bacteraemia (S. pneumoniae, n = 15; N. meningitidis, n = 2; Klebsiella pneumoniae, n = 1); 12 male, 6 female.

11/18 had no focal signs of infection; 7/18 had signs or symptoms of upper respiratory tract infection (n = 4) or otitis media (n = 3)

6/18 were admitted to hospital (for febrile convulsions, n = 2; for suspected UTI, n = 1; for WCC ≥20x10^9/L, n = 3)

Final diagnosis of 18 children serious illness :Bacteraemia, n = 12, Otitis media, n = 3, Periorbital cellulitis, n = 1, UTI, n = 1, Pneumonia, n = 1

Table :Comparison with children without bacteraemia, mean (SD)
<table>
<tr><th></th><th>Bacteraemia (n = 18)</th><th>No bacteraemia (n = 516)</th><th>P value</th></tr>
<tr><td>Age (months)</td><td>17.6 (9.4)</td><td>16.4 (7.9)</td><td>0.56</td></tr>
<tr><td>Fever (°C)</td><td>39.7 (0.39)</td><td>39.7 (0.55)</td><td>0.91</td></tr>
<tr><td>McCarthy Score</td><td>7.0 (1.5)</td><td>7.4 (1.9)</td><td>0.45</td></tr>
<tr><td>WCC</td><td>22.1 (7.7)</td><td>15.0 (8.2)</td><td>< 0.001</td></tr>
<tr><td>Absolute neutrophil count</td><td>13.7 (6.5)</td><td>8.6 (7.9)</td><td>0.007</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Citation/EI</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>Demographic and clinical details taken; general condition assessed on McCarthy Observation Scale, where score ≤10 is associated with low risk of serious illness; and likelihood of bacteraemia predicted by medical staff (1–2 = unlikely; 3 = unsure; 4–5 = likely). Full blood count and culture taken and final diagnosis of illness determined by one investigator

Bacteraemia diagnosed if blood culture showed growth of a pathogenic organism.</td><td>
<table>
<tr><td>Total band count</td><td>2.5 (2.0)</td><td>1.6 (1.6)</td><td>0.63</td></tr>
</table>

Children with fever of 12 hours or less duration were more likely to have bacteraemia than those who had fever longer (10/103 v. 8/411; RR 4.6, 95% CI 1.8 to 12, P< 0.001); predictive accuracy of fever < 12hrs for occult bacteraemia was 9.4% (95% CI 4.8 to 16).

Referral source did not predict bacteraemia (7/118 from GP v. 11/398 self-referred; RR 2.1, 95% CI 0.8 to 5.3)

128/534 (24%) had WCC count ≥20.0 x 10^9/L; these children had 5 fold increased risk of bacteraemia (95% CI 2.0 to 13, P< 0.001), but using this threshold to start empiric treatment resulted in sensitivity 61% (95% CI 36 to 83), specificity 77% (95% CI 73 to 81) and PPV 9.4% (95% CI 4.8 to 16)
</td></tr>
<tr><td>Berger[129]

<u>Study type:</u>
Prospective cohort study.

EL 2+</td><td><u>County:</u>
Netherlands
<u>Aim:</u>
To determine independent predictors of SBIs in febrile infants.
<u>Method, inclusion/exclusion:</u>
All infants aged 2 weeks to 1 year, presenting during a 1-year-period with rectal temperature ≥ 38.0 °C to the Sophia Children’s Hospital were included. Infants with a history of prematurity, perinatal complications, known underlying disease, antibiotic treatment or vaccination during the preceding 48 hours were excluded. Clinical and laboratory variables at presentation were evaluated by a multivariate logistic regression model</td><td>Of the 138 infants included in the study, 33 (24%) had SBI. Logistic regression analysis defined C-reactive protein (CRP), duration of fever, standardized clinical impression score, a history of diarrhoea and focal signs of infection as independent predictors of SBIs (values of one of the variables were missing in 24 infants).

Table : the independent factors associated with increased risk of SBIs
<table>
<tr><td>Variable</td><td>Coefficient (n = 67)*</td><td>OR</td><td>95% CI</td></tr>
<tr><td>CRP (mg/ml)</td><td>0.03</td><td>1.03</td><td>1.01–1.05</td></tr>
<tr><td>Duration of fever > 48 hr</td><td>1.35</td><td>3.85</td><td>1.11–13.3</td></tr>
<tr><td>YOS (0–8)</td><td>0.20</td><td>1.22</td><td>0.95–1.57</td></tr>
<tr><td>History of diarrhoea</td><td>1.15</td><td>3.15</td><td>0.97–10.2</td></tr>
<tr><td colspan="4">* Infants with focal signs of infection</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EI</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>using SBI as the dependent variable.</td><td></td></tr>
<tr><td>Hsiao[126]

<u>Study type:</u>
Prospective cohort study.

EL 2+</td><td><u>Country:</u>
USA
<u>Aim:</u>
To investigate aetiology of fever and usefulness of screening tests in older (2–6 months) infants.
Method:
It’s a prospective study of febrile infants 57–180 days old. Evaluation included blood and urine tests and direct fluorescent antibody (DFA) of nasal swabs for respiratory viruses. Additional studies were performed at the discretion of managing clinicians.</td><td>Serious bacterial illness (SBI) was diagnosed in 44 (10.3%) of 429 infants: 41 with bacteriuria and 4 with bacteraemia (1 infant had concurrent Escherichia coli bacteriuria and bacteraemia). Lumbar puncture, performed in 58 (13.5%) infants, revealed no cases of bacterial meningitis. DFAs were positive in 163 (38.0%) infants: the majority were RSV or influenza A. SBI was noted in 4.9% of infants with positive DFA. Height of fever were not significant predictors of SBI (38.4±1.0 vs. 38.5±0.8; P = 0.18). Duration of fever was longer in infants with SBIs (18.6±21.7 hr) than those without (26.5±41.5hr) (P< 0.01). White blood cell count (17.1 K/mm3 vs. 12.4 K/mm3) and CRP (2.6 mg/dL vs. 0.9 mg/dL) were elevated in infants with SBI, as was the Yale Observation Score (9.4 vs. 8.0).</td></tr>
<tr><td>Trautner[130]

<u>Study type:</u>
Prospective cohort study.

EL 2+</td><td><u>Country:</u>
USA
<u>Aim:</u>
To determine (1) the risk of serious bacterial infection in children with hyperpyrexia and (2) whether clinical presentation can identify hyperpyrexic patients at risk for serious bacterial infection
<u>Method:</u>

Data were collected prospectively on</td><td>Of 130828 visits, 103 children had hyperpyrexia (1 per 1270 patient visits). Of the 103 subjects, 20 had serious bacterial infection, and 22 had laboratory-proven viral illness (including 1 subject with bacterial/viral co-infection). The presence of a chronic underlying illness was associated with an increased risk of serious bacterial infection. The presence of rhinorrhoea or any viral symptom was associated with a decreased risk of serious bacterial infection, although diarrhoea itself was associated with an increased risk of serious bacterial infection. Age, maximum temperature, and total white blood cell count were not predictive of either bacterial or viral illness. SBI was defined as the growth of a clinically significant bacterial pathogen from blood, urine, stool, CSF, or any normally sterile body site.
The details are in the table below:
Table : Predictive values for the duration of fever of SBI
<table>
<tr><td>Variable</td><td>Frequency; N (%)</td><td>OR (95% CI)</td></tr>
<tr><td>Duration of fever; hour</td><td></td><td></td></tr>
<tr><td>< 24</td><td>8 (40)</td><td>1</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/El</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>all children < 18 years of age presenting to a paediatric emergency department during a 2-year period with rectal temperatures of ≥ 106 degrees F. History, physical examination, complete blood cell counts, blood cultures, and nasopharyngeal viral cultures were obtained on all of the patients.</td><td>
<table>
<tr><td>24–48</td><td>3 (15)</td><td>0.30 (0.07–1.26)</td></tr>
<tr><td>> 48</td><td>9 (45)</td><td>1.04 (0.35–3.12)</td></tr>
</table>
</td></tr>
<tr><td>Bleeker[151]

<u>Study type:</u>
Retrospective data analysis

EL 3</td><td><u>County:</u>
Netherlands
<u>Aim</u>
To design a clinical rule to predict the presence of a serious bacterial infection in children with fever without apparent source.
<u>Method, inclusion/exclusion:</u>
Information was collected from the records of children aged 1–36 months who attended the paediatric emergency department because of fever without source (temperature ≥38 °C and no apparent source found after evaluation by a general practitioner or history by a paediatrician). Serious bacterial infection included bacterial meningitis, sepsis, bacteraemia, pneumonia, urinary tract infection, bacterial gastroenteritis, osteomyelitis and ethmoiditis.</td><td>They enrolled 231 patients (mean age 1.1 y) and 25% of them had a serious bacterial infection. Independent predictors from history and examination included duration of fever, poor micturition, vomiting, age, temperature < 36.7 °C or ≥40 °C at examination, chest-wall retractions and poor peripheral circulation (ROC area: 0.75, other detail not provided). Independent predictors from laboratory tests were white blood cell count, serum C-reactive protein and the presence of > 70 white blood cells in urinalysis (ROC area: 0.83). The risk stratification for serious bacterial infection ranged from 6% to 92%.
<table>
<tr><td></td><td colspan="2">Clinical model</td><td colspan="2">Clinical + Lab model</td></tr>
<tr><td>Features</td><td>Regression coefficient</td><td>OR (90%CI)</td><td>Regression coefficient</td><td>OR (90%CI)</td></tr>
<tr><td>Duration of fever (d)</td><td>0.91</td><td>2.5 (0.8–7.5)</td><td>0.31</td><td>1.4 (0.4–5.1)</td></tr>
<tr><td>Temperature < 36.7 °C or ≥40 °C</td><td>0.52</td><td>1.7 (0.9–3.0)</td><td>0.54</td><td>1.7(0.8–3.5)</td></tr>
<tr><td>ROC area (95% CI)</td><td>--</td><td>0.75 (0.68–0.83)</td><td>--</td><td>0.83 (0.77–0.89)</td></tr>
</table>
</td></tr>
<tr><td>Goh[154]</td><td><u>Country:</u></td><td>Of 86 enrolled children, 17 (19.8 percent) had serious bacterial infection. Duration of fever and white blood cell count were found to be significant predictors. Children with white blood cell count equal to or greater than 16,000/cubic mm had</td></tr>
</table>

Citation/EI	Method	Results
Study type: Retrospective data analysis EL 3	Singapore Aim: To identify predictors of serious bacterial infection in children aged between 3 to 36 months with fever without source. Method, inclusion/exclusion: Inpatient records of all children aged three to 36 months admitted from the Emergency Department of Singapore's main paediatric hospital between October 2001 to February 2002 with International Classification of Diseases (9th revision) diagnosis codes 038 (septicaemia), 079 (viral fever), or 780 (pyrexia of unknown origin), were retrieved and reviewed. Patients identified as having fever without source were enrolled.	6.9 times (95 percent confidence interval [CI] is 1.7 to 28.4) increased risk of serious bacterial infection, while children with fever of duration > 3 days before presentation had 3.8 times (95 percent CI is 1.1 to 13.1) increased risk of serious bacterial infection. A combination of white blood cell count less than 16,000/cubic mm and duration of fever three days or less had a negative predictive value of 1.0 (95 percent CI is 0.88 to 1.0) and a sensitivity of 1.0 (95 percent CI is 0.82 to 1.0).

Review question 7

In children with fever, what symptoms or combination of symptoms are associated with serious illness* or mortality? (Possibly stratified by age group e.g. 0–3 months; 3–12 months; 1–5 years)

Sub-questions

Are there any scoring systems that use symptoms in children with fever to predict the risk of serious illness? How accurate are they? (e.g. Yale and Rochester scales, Sensitivity/specificity/PPV/NPV) In children with fever, what symptoms are associated with self-limiting illness?

Review question 8

In children with fever, what signs or combination of symptoms and signs are associated with serious illness* or mortality? (Possibly stratified by age group e.g. 0–3 months; 3–12 months; 1–5 years)

Sub-questions

Are there any scoring systems that use symptoms and signs in children with fever to predict the risk of serious illness? How accurate are they? (e.g. Yale and Rochester scales, Sensitivity/specificity/PPV/NPV)

In children with fever, what symptoms and signs are associated with self-limiting illness?

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr>
<td>Baraff[163]

study type:
Systematic review and meta-analysis

EI: 2+</td>
<td>Aim:
They aimed to determine the prevalence of meningitis, bacteraemia and all SBIs in the febrile infants < 3 months according to commonly used clinical and lab factors. Moreover, to identify the nature and aetiology of SBIs in this age group to determine the outpatient management.
Method:
They searched English language literature using MEDLINE from 1972 to May 1991. They only included original studies concerning febrile infants < 3 months. SBI was defined as sepsis, meningitis, bacteraemia, pneumonia, UTI, bacterial enteritis, septic arthritis and osteomyelitis.</td>
<td>They used hierarchical Bayesian meta-analysis to combine data from individual publications.
The mean risk of bacteraemia of the individual studies ranged from 0–3.2%, the mean of the probability distribution of the combined studies was 1.4% and the upper limits of the 95% CI was 2.7%. The results also showed that the classification of Rochester criteria results in two populations at significantly different risk of bacteraemia.

Table : Hierarchical Bayesian meta-analysis: probability of bacterial infections in infants ≤ months of age as a function of clinical and lab findings*
<table>
<tr><td></td><td colspan="5">% of patients</td></tr>
<tr><td></td><td>Rochester</td><td>Low risk**</td><td>Non-toxic</td><td>Toxic</td><td>High risk</td></tr>
<tr><td>SBI</td><td>1.4 (0.4–2.7)</td><td>2.6 (1.5–4.0)</td><td>8.6(3.7–15.6)</td><td>17.3 (8.0–30.0)</td><td>24.3 (18.2–31.4)</td></tr>
<tr><td>Bacteraemia</td><td>1.1 (0.2–2.6)</td><td>1.3 (0.8–2.1)</td><td>2.0 (0.8–3.8)</td><td>10.7 (6.7–15.7)</td><td>12.8 (7.3–19.9)</td></tr>
<tr><td>Meningitis</td><td>0.5 (0.0–1.0)</td><td>0.6 (0.3–1.0)</td><td>1.0 (0.2–2.4)</td><td>3.9 (1.7–7.1)</td><td>3.9 (1.7–7.0)</td></tr>
</table>
*: numbers in parentheses, 95% CI of the probability distribution.
** low risk were defined as previously healthy, non-toxic appearance, no focal bacterial infection on physical exam and negative lab screening. If the authors defined the low risk differently, they re-classified infants to meet the criteria</td>
</tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td></td><td>whenever possible.

There was no overlap of the 95% credible sets of the low and high risk groups for the infectious groups. The relative risk of the mean risks of each of the infections between the high and low risk groups is SBI 9.3, bacteraemia 9.8, and meningitis 6.5.</td></tr>
<tr><td>Hewson[93]

<u>study type:</u>
prospective cohort study
EL:2+</td><td><u>Country:</u>
Australia
<u>Aim:</u>
To perform a multicentre follow-up study to determine if previously identified markers of serious illness in early infancy were robust and statistically reliable.
<u>Setting, inclusion/exclusion:</u>
This study was conducted from July 1991 to June 1992. This was a study on the clinical marks of serious illness in young infants aged 1-to 26 weeks presenting to the Emergency Departments of Royal Children’s Hospital and two general Melbourne metropolitan Hospitals for 12 months.
Rectal temperature was used in this study. Type of thermometer is not specified. The predictive values of temp. < 36.4 °C, > 38.0 °C and > 38.9 °C were explored. Exclusion criteria were not reported
Clinical markers:
13. Drowsiness
(a) occasional</td><td>From 3806 assessments (mean age: 77 days. 62.4% were < 13 weeks) there were 312 infants assessed as being seriously ill (8.2%).
Table :The diagnostic values of the markers of serious illness for all infants from 0–26 weeks.
<table>
<tr><th></th><th>No.</th><th>PPV (%)</th><th>NPV (%)</th><th>Relative risk</th><th>Sensitivity (%)</th><th>Specificity (%)</th></tr>
<tr><td>Drowsiness
(a) occasional
(b) frequent
(c) on examination
(d) any (history or on exam)</td><td>
219
32
26
262</td><td>
27.4
59.4
57.7
32.1</td><td>
93.0
92.2
92.1
93.6</td><td>
3.91
7.62
7.30
5.02</td><td>
19.2
6.1
4.8
26.9</td><td>
95.4
99.6
99.7
94.9</td></tr>
<tr><td>Decreased activity</td><td>37</td><td>45.9</td><td>92.2</td><td>5.88</td><td>5.4</td><td>99.4</td></tr>
<tr><td>(a) difficult breathing
(b) moderate – severe chest wall recession</td><td>484
84</td><td>10.7
40.5</td><td>92.2
92.5</td><td>1.37
5.4</td><td>16.7
10.9</td><td>87.6
98.6</td></tr>
<tr><td>(a) pale on history
(b) pallor on exam</td><td>134
63</td><td>32.1
49.2</td><td>92.7
92.5</td><td>4.40
6.56</td><td>13.8
9.9</td><td>97.4
99.1</td></tr>
<tr><td>(a) feeding 2/3–1/2
(b) feeding < 1/2</td><td>647
195</td><td>14.5
30.8</td><td>93.1
93.0</td><td>2.07
4.40</td><td>30.1
19.2</td><td>84.2
96.1</td></tr>
<tr><td>Urine output:< 4 wet nappies</td><td>98
196</td><td>31.6
16.8</td><td>92.3
92.4</td><td>4.10
2.21</td><td>9.9
10.6</td><td>98.1
95.3</td></tr>
<tr><td>Convulsion</td><td>33</td><td>27.3</td><td>90.8</td><td>2.97</td><td>3.5</td><td>99.0</td></tr>
</table></td></tr>
</table>

Citation/EL	Method	Results

(b) frequent
(c) on examination
(d) any (history or on exam)

14. Decreased activity

15. (a) difficult breathing
(b) moderate – severe chest wall recession

16. (a) pale on history
(b) pallor on exam

17. (a) feeding 2/3–1/2
(b) feeding < 1/2

18. Urine output

19. Vomits: > 5/24 hr

20. Convulsion

21. Bile-stained vomiting

22. Respiratory grunt

23. Lump > 2 cm

24. Temp. (RT, type of thermometer not reported)
(a) 38.1–38.9 °C
(b) > 38.9or < 36.4 °C
(c) > 38.1 or < 36.4 °C

<u>Definition of serious illness:</u>

Either having a serious investigation result (i.e. positive pathological bacterial culture from blood, urine, CSF, faeces, or a chest-x ray reported as showing consolidation in a febrile patient) or by requiring significant treatment in hospital as supervised by independent staff (i.e. NG or IV fluid, parental antibiotics,

Bile-stained vomiting	17	47.1	90.8	5.12	3.1	99.6
Respiratory grunt	46	19.6	90.7	2.11	3.5	98.5
Lump > 2 cm	180	41.7	92.6	5.64	31.9	95.8
Temp. (a) 38.1–38.9 °C (b) > 38.9or < 36.4 °C (c) > 38.1 or < 36.4 °C	 252 101 353	 29.0 41.6 32.6	 92.2 91.7 93.0	 3.62 5.13 4.71	 17.5 10.1 27.6	 95.8 98.6 94.4

Table :The cumulative diagnostic values of the markers of serious illness*.

	Cumulative Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Relative risk
Drowsiness	26.9	94.4	32.1	93.6	5.02
Pale on history or exam	36.9	92.6	30.7	94.3	4.58
Difficult breathing	50.0	97.7	19.1	94.8	3.67
Temp. > 38.1 or < 36.4 °C	62.2	76.8	18.9	95.5	4.2
Lump	82.5	73.5	22.1	97.7	9.61
Feeding < 1/2	83.9	71.8	21.3	97.8	9.68
> 5 vomits/24 hr	87.3	68.5	20.1	98.2	11.2
< 4 wet nappies/24 hr	87.9	68.2	20.1	98.3	11.8

 excluding infants with inguinal hernia.

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>O2 > 30% or surgery).</td><td>Data collection was not blind, randomised and didn't report the measurements of reference standard before and after intervention. Control Group: not reported. No details of follow-up although this study was claimed as multicentre follow-up study. The sensitivity, specificity, positive predictive value and negative predictive value were used for statistical analysis but 95% CI did not report. The risk of bias on this study was likely to affect the result although the study related to infant with fever.</td></tr>
<tr><td>Nademi[121]

Study type
Prospective cohort study

EL:2+</td><td>Country:
UK.
Aim:
To assess the causes of fever and identify clinical and laboratory features suggesting serious disease in U.K.
Setting, inclusion/exclusion:
This study was conducted in August and October 1999
All patients presenting fever to the paediatric assessment units at Newcastle General Hospital. Children presenting to hospital with temperatures ≥38 °C were included and patients with a temp. < 38 °C were excluded.
Definition of serious illness: sepsis, meningitis, toxic shock syndrome, brain abscess, pneumonia, UTI, ischiorectal abscess, appendicitis.
Twenty two (16%) had already received antibiotics (usually amoxicillin) within last 24 h, including 8 serious illness.</td><td>One hundred and forty one children between 8 days and 16 years of age (mean age 3.3 years) were studied, 64% male, 55% aged under 2 years. Serious disease was present in 41 (29%) with 31 (22%) microbiologically or radiologically proven and the other 10 given a diagnosis of sepsis cause including three patients with clinical signs of meningococcal disease but without any positive culture.
35/41 (86%) of patients with serious bacterial infections had temperatures between 38 and 39 °C and 3 (7%) had temperature between 38–39 °C. Ninety six percent were casualty or GP referrals and 4% were tertiary referrals. Twenty nine percent (41/141) had serious disease but microbiologically or radiologically proven in only 22% (31/141); pneumonia (nine), meningitis (seven), sepsis (five), urinary tract infection (five), brain abscess (two), toxic shock syndrome (one), appendicitis (one), ischiorectal abscess (one). Forty two percent (5/12) of microbiologically proven meningitis and sepsis and 36% (8/22) of all meningitis and sepsis were meningococcal. 71% had non-serious diseases.
Table :Comparison of sensitivity, specificity, PPV and NPV of all variables with 95% CI to detect serious illness (n = 41)
<table>
<tr><th></th><th>Sensitivity %</th><th>Specificity %</th><th>PPV %</th><th>NPV %</th><th>Relative risk</th></tr>
<tr><td>T> 39 °C.</td><td>14 (3–25)</td><td>82 (74–89)</td><td>25 (7–42)</td><td>70 (61–78)</td><td>0.83</td></tr>
<tr><td>T> 39.5 °C.</td><td>7 (0–15)</td><td>93 (87–98)</td><td>30 (1–58)</td><td>71 (63–78)</td><td>1.03</td></tr>
<tr><td>Poor feeding</td><td>78 (65–90)</td><td>43 (33–52)</td><td>36 (25–45)</td><td>83 (72–92)</td><td>2.12</td></tr>
<tr><td>Vomiting</td><td>59 (43–73)</td><td>60 (50–69)</td><td>38 (25–49)</td><td>78 (68–87)</td><td>1.73</td></tr>
<tr><td>Restlessness</td><td>76 (62–88)</td><td>43 (33–52)</td><td>35 (25–45)</td><td>81 (70–91)</td><td>1.84</td></tr>
<tr><td>Petechial rash</td><td>29 (15–43)</td><td>98 (95–1000</td><td>86 (67–100)</td><td>77 (69–84)</td><td>3.74</td></tr>
<tr><td>WBC</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>> 15 000</td><td>10 (0.6–18)</td><td>95 (90–990</td><td>44 (11–76)</td><td>72 (64–79)</td><td>2.44</td></tr>
<tr><td>> 20 000</td><td>29 (15–43)</td><td>93 (87–98)</td><td>63 (41–84)</td><td>76 (68–83)</td><td>2.63</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>Axillary temperature was measured routinely in children < 3yr; tympanic temperature in children > 3yr. Type of thermometer not specified.</td><td></td></tr>
<tr><td>Weber[98]

<u>Study type:</u>
prospective cohort study
EL: 2+</td><td><u>Country:</u>
Ethiopia, the Gambia. Papua New Guinea and the Philippines.
<u>Aim:</u>
To identify simple procedures for identifying infants with infection that need referral for treatment are therefore of major public health importance.
<u>Setting, inclusion/exclusion:</u>
At hospitals or outpatient clinics where large number of sick infants were seen from April 1978 to March 1979.
Rectal temperature for children < 5; oral temperature for > 5 years. Type of thermometer not reported.
At each study site, infants < 91 days of age seen consecutively for acute care with chief complaints indicating possible infection were eligible. This report only analyse the age group 0–59 days. Entry criteria were intended to include a wide spectrum of illness severity and to ensure that virtually all infants with serious infection would be included.
Children with congenital heart</td><td>They recruited 3303 infants < 2 mo.
Level 0: No abnormality, n = 2585 (78.3%); level 1: Mild hypoxemia (90%≤SaO2< 95%) or radiologic pneumonia; n = 346 (10.5%); and level 2: Severe hypoxemia (SaO2< 90%) or bacteraemia or meningitis: n = 372 (11.3%); and 194 (5.9%) died. There were 120 cases of sepsis, 34 of meningitis and 259 of hypoxemia.

Table : Independently significant predictors of Ordinal Outcome 1 or 2vs 0 in the three groups of general status, respiratory signs and meningitis signs, for the age group 0–6 days.

<table>
<tr><th>Signs or symptom</th><th>Prevalence (%)</th></tr>
<tr><td>General status</td><td></td></tr>
<tr><td>• Feeding ability reduced</td><td>17*</td></tr>
<tr><td>• No spontaneous movement</td><td>11*</td></tr>
<tr><td>• Temp. > 38 °C</td><td>19*</td></tr>
<tr><td>• Drowsy</td><td>7</td></tr>
<tr><td>• History of feeding problem</td><td>16</td></tr>
<tr><td>• Hx of change in activity</td><td>21</td></tr>
<tr><td>• Agitated</td><td>4</td></tr>
<tr><td>• Digital capillary refill</td><td>11*</td></tr>
<tr><td>Respiratory signs</td><td></td></tr>
<tr><td>• Lower chest wall indrawing</td><td>14*</td></tr>
<tr><td>• Res rate > 6</td><td>23*</td></tr>
<tr><td>• Grunting</td><td>2*</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>disease and hypoxemia were excluded.

All infants underwent a standardized history and physical exam to assess the degree of signs and symptoms. All had and pulse oximetry. Infants with pre-specified symptoms associated with bacterial infection had lab evaluation that included blood culture, WBC, CXR (n = 1809). Specific criteria were used to identify infants for lumbar puncture (n = 401).

Definition of sepsis:

The growth of an unknown pathogen in cultures of blood.

Ranking of disease severity:

Level 0: No abnormality

Level 1: Mild hypoxemia (90%≤SaO_2< 95%) or radiologic pneumonia.

Level 2: Severe hypoxemia (SaO_2< 90%) or bacteraemia or meningitis.

Death was separately analysed.</td><td>
<table>
<tr><td>• Cyanosis</td><td>4*</td></tr>
<tr><td>Meningitis signs</td><td></td></tr>
<tr><td>• Hx of convulsion</td><td>4*</td></tr>
<tr><td>• Bulging fontanel</td><td>2</td></tr>
</table>
*: these signs comprise a restricted group that were considered for a more specific diagnostic algorithm, (see next table)

Table :Sensitivity, specificity and negative likelihood ratio of different combination rules for predicting severe illness by ordinal outcome scale (0 vs. 1+2)
<table>
<tr><td></td><td colspan="2">0–59 days</td><td colspan="2">0–6 days</td><td colspan="2">7–59 days</td></tr>
<tr><td rowspan="2">Any sign of previous table</td><td>Sn 87</td><td>LR+1.89</td><td>Sn 95</td><td>LR+1.28</td><td>Sn 85</td><td>LR+1.98</td></tr>
<tr><td>Sp 54</td><td>LR- 0.24</td><td>Sp 26</td><td>LR- 0.19</td><td>Sp 57</td><td>LR- 0.26</td></tr>
<tr><td rowspan="2">Any one sign from list of 9 marked† in the previous table</td><td>Sn 83</td><td>LR+2.18</td><td>Sn 92</td><td>LR+1.31</td><td>Sn 82</td><td>LR+2.28</td></tr>
<tr><td>Sp 62</td><td>LR- 0.27</td><td>Sp 30</td><td>LR- 0.27</td><td>Sp 64</td><td>LR- 0.28</td></tr>
<tr><td rowspan="2">Any sign omitting resp rate (n = 13)</td><td>Sn 80</td><td>LR+2.05</td><td>Sn 94</td><td>LR+1.32</td><td>Sn 78</td><td>LR+2.11</td></tr>
<tr><td>Sp 61</td><td>LR- 0.33</td><td>Sp 29</td><td>LR- 0.21</td><td>Sp 63</td><td>LR- 0.35</td></tr>
<tr><td rowspan="2">Feeding ability: reduced or lower chest indrawing or history of convulsion (n = 3, most predictive signs only)</td><td>Sn 60</td><td>LR+3.53</td><td>Sn 80</td><td>LR+1.60</td><td>Sn 56</td><td>LR+3.73</td></tr>
<tr><td>Sp 83</td><td>LR- 0.48</td><td>Sp 50</td><td>LR- 0.40</td><td>Sp 85</td><td>LR- 0.52</td></tr>
</table>
</td></tr>
</table>

Citation/EL	Method	Results

Any 1 sign from general status + I from other group	Sn 51	LR+3.92	Sn 65	LR+1.76	Sn 48	LR+4.00
	Sp 87	LR- 0.56	Sp 63	LR- 0.56	Sp 88	LR- 0.59
Any 2 signs	Sn 69	LR+3.00	Sn 87	LR+1.47	Sn 66	LR+3.14
	Sp 77	LR- 0.40	Sp 41	LR- 0.32	Sp 79	LR- 0.43
Any 1 sign if wt < 3kg or any 2 signs if wt> 3kg	Sn 72	LR+2.88	Sn 91	LR+1.36	Sn 68	LR+3.09
	Sp 75	LR- 0.37	Sp 33	LR- 0.27	Sp 78	LR- 0.41
Fever (temp.> 38 °C) and any other sign	Sn 25	LR+2.78	Sn 21	LR+1.31	Sn 26	LR+3.25
	Sp 91	LR- 0.82	Sp 84	LR- 0.94	Sp 92	LR- 0.80

*: Sn: sensitivity, Sp: specificity, LR+: positive likelihood ration; LR-: negative likelihood ratio.

Table :Association of clinical signs with sepsis, meningitis, hypoxemia and death. OR adjusted for place of study, weight and age.

		Sepsis		Meningitis	
	Prevalence (%)	OR	95% CI	OR	95% CI
Hx of cough	75	--	--	--	--
Hx of fast breathing	35	--	--	--	--
Hx of change in level of activity	21	3.6	2.5–5.1	6.4	3.1–13.5
Hx of change of crying	38	1.9	1.4–2.7	2.1	1.1–4.1

Citation/EL	Method	Results					
		Hx of convulsion	4	4.2	2.6–7.0	12.2	6.2–23.9
		Hx of feeding problem	15	3.9	2.6–5.7	6.0	3.0–12.4
		Lower chest wall indrawing	14	1.5	1.0–2.2	--	--
		Nasal flaring	4	1.6	0.8–2.9	--	--
		Grunting	3	2.8	1.5–5.1	3.7	1.3–10.1
		Crepitations	17	1.3	0.9–2.0	--	--
		Wheeze	11	0.6	0.3–1.2	--	--
		Drowsy/unconscious	7	3.0	2.0–4.7	4.6	2.2–9.6
		Agitated	5	2.4	1.5–4.0	3.8	1.7–8.4
		Lethargy	16	2.3	1.6–3.3	2.4	1.2–4.7
		Feeding ability reduced	15	5.1	3.4–7.7	8.1	3.7–17.9
		No spontaneous movement	10	3.0	2.0–4.6	3.6	1.7–7.5
		Consolability: continues to cry/fuss	4	2.9	1.8–4.8	3.4	1.3–8.6
		Central cyanosis	3	2.4	1.3–4.3	2.0	0.6–6.5
		Dehydration	7	1.1	0.7–1.9	--	--
		Digital capillary refill 2+s	11	2.2	1.5–3.3	1.7	0.8–3.4
		Umbilical discharge	4	1.1	0.5–2.3	--	--
		Bulging fontanel	2	10.0	5.6–18.0	21.4	10.0–45.8
		Resp rate < 40	19	1.2	0.8–1.9	1.3	0.6–3.0
		Resp rate ≥60	23	2.2	1.5–3.1	2.0	1.0–4.1
		Temp. < 35.5	2	3.7	1.8–7.3	4.2	0.8–22.5

Citation/EL	Method	Results

Temp.≥ 38	17	3.6	2.6–5.1	11.8	5.7–24.6
Hypoxemia	8	2.3	1.5–3.7	1.7	0.7–4.2
Invasive bacterial infection	4	--	--	--	--
Meningitis	1	--	--	--	--
		Hypoxemia		Death	
	Prevalence (%)	OR	95% CI	OR	95% CI
Hx of cough	75	1.5	1.1–2.0	--	--
Hx of fast breathing	35	3.6	2.7–4.7	--	--
Hx of change in level of activity	21	3.2	2.5–4.2	3.7	2.7–5.1
Hx of change of crying	38	1.7	1.3–2.1	1.0	0.8–1.4
Hx of convulsion	4	1.5	0.9–2.6	5.3	3.4–8.3
Hx of feeding problem	15	2.9	2.2–3.9	4.6	3.3–6.4
Lower chest wall indrawing	14	6.4	4.9–8.4	2.8	2.0–3.9
Nasal flaring	4	6.8	4.5–10.1	3.8	2.5–5.9
Grunting	3	4.5	2.8–7.3	5.1	3.1–8.3
Crepitations	17	9.5	7.1–12.7	1.9	1.3–2.8
Wheeze	11	2.2	1.5–3.1	0.9	0.6–1.5
Drowsy/unconscious	7	6.1	4.4–8.4	8.0	5.7–11.2
Agitated	5	3.1	2.0–4.7	1.3	0.8–2.2
Lethargy	16	3.8	2.9–5.0	4.5	3.3–6.1
Feeding ability	15	7.9	5.8–10.7	8.9	6.1–13.0

Citation/EL	Method	Results

reduced					
No spontaneous movement	10	5.3	3.9–7.1	7.7	5.6–10.7
Consolability: continues to cry/fuss	4	4.0	2.5–6.2	4.7	3.0–7.3
Central cyanosis	3	15.0	9.9–22.6	5.7	3.6–8.8
Dehydration	7	--	--	1.8	1.2–2.6
Digital capillary refill 2+s	11	2.7	1.9–3.7	3.4	2.4–4.6
Umbilical discharge	4	--	--	1.7	0.9–3.0
Bulging fontanel	2	--	--	5.5	2.9–10.4
Resp rate < 40	19	1.1	0.7–1.7	1.7	1.2–2.5
Resp rate ≥60	23	4.5	3.3–6.2	2.3	1.6–3.3
Temp. < 35.5	2	3.2	1.9–5.4	3.1	1.8–5.3
Temp.≥ 38	17	2.4	1.7–3.2	2.3	1.7–3.2
Hypoxemia	8	--	--	4.5	3.0–6.7
Invasive bacterial infection	4	--	--	5.2	3.3–8.2
Meningitis	1	--	--	11.0	5.1–23.5

Table :Association of clinical signs with the age group 0–6 days. OR adjusted for the place of study.

	Age group 0–6 days				
		Outcome: level 1 or 2 (cf.0)		Outcome: level 2 (cf.0 or 1)	
	Prevalence (%)	OR	95% CI	OR	95% CI
Hx of cough	18	1.9	0.8–4.3	0.9	0.3–2.5

Citation/EL	Method	Results					
		Hx of fast breathing	38	2.5	1.5–4.3	1.9	1.1–3.5
		Hx of change in level of activity	31	1.4	0.8–2.4	1.6	0.8–3.0
		Hx of change of crying	30	1.3	0.7–2.1	1.6	0.9–2.9
		Hx of convulsion	9	1.0	0.4–2.4	1.0	0.4, 2.5
		Hx of feeding problem	48	1.9	1.1–3.4	3.6	1.7, 7.6
		Hx of diarrhoea	11	0.4	0.2–0.9	0.3	0.1, 1.0
		Lower chest wall indrawing	20	1.9	1.0–3.6	2.4	1.2–4.7
		Nasal flaring	12	1.6	0.7–3.4	2.1	0.9–4.8
		Grunting	9	1.9	0.8–4.5	1.6	0.6–3.9
		Crepitations	6	7.2	2.0–26.3	3.3	1.1–9.3
		Wheeze	5	0.6	0.2–1.9	0.8	0.2–3.1
		Drowsy/unconscious	21	3.7	2.0–6.9	3.4	1.8–6.5
		Agitated	7	1.2	0.5–3.3	1.5	0.5–4.3
		Lethargy	40	1.5	0.9–2.5	2.1	1.2–3.9
		Feeding ability reduced	57	5.0	2.5–9.9	4.6	2.0–10.7
		No spontaneous movement	37	1.8	1.1–3.1	2.4	1.3–4.3
		Consolability: continues to cry/fuss	12	1.8	0.7–4.3	1.5	0.7–3.7
		Central cyanosis	9	3.5	1.4–8.4	4.0	1.7–9.3
		Dehydration	10	1.2	0.5–2.7	1.6	0.7–3.7
		Digital capillary refill	23	2.9	1.6–5.2	1.7	0.9–3.2

Citation/EL	Method	Results

2+s					
Skin rash	9	0.3	0.1–1.7	0.5	0.0–4.3
Umbilical discharge	17	1.4	0.7–2.8	1.1	0.5–2.6
Bulging fontanel	3	1.5	0.4–6.3	1.6	0.4–6.9
Eye discharge	10	1.7	0.7–4.2	1.7	0.5–5.2
Jaundice	45	0.7	0.4–1.2	0.8	0.4–1.4
Resp rate < 40	21	1.8	0.9–3.5	3.4	1.5–7.7
Resp rate ≥60	37	1.8	1.0–3.3	2.2	1.1–4.6
Temp. < 35.5	15	2.0	0.9–4.2	2.1	0.9–4.8
Temp.≥ 38	22	1.0	0.5–1.9	1.1	0.5–2.2

Table :Association of clinical signs with the age group 7–60 days. OR adjusted for the place of study and weight.

	Age group 7–60 days				
		Outcome: level 1 or 2 (cf.0)		Outcome: level 2 (cf.0 or 1)	
	Prevalence (%)	OR	95% CI	OR	95% CI
Hx of cough	76	1.1	0.9–1.4	0.7	0.6–0.9
Hx of fast breathing	34	2.6	2.2–3.2	2.5	2.0–3.3
Hx of change in level of activity	20	3.6	2.9–4.5	5.0	3.7–6.6
Hx of change of crying	37	1.3	1.1–1.6	1.4	1.1–1.9
Hx of convulsion	4	4.0	2.7–6.0	4.9	3.1–7.6
Hx of feeding	12	2.9	2.3–3.7	3.9	2.9–5.2

Citation/EL	Method	Results

problem						
Hx of diarrhoea	17	0.7	0.6–1.0	0.8	0.6–1.1
Lower chest wall indrawing	13	5.6	4.4–7.0	3.9	2.9–5.1
Nasal flaring	4	6.9	4.5–10.8	4.5	2.9–6.9
Grunting	2	8.1	4.4–15.1	5.7	3.2–10.2
Crepitations	16	7.3	5.8–9.2	4.7	3.6–6.2
Wheeze	9	2.3	1.7–3.1	1.3	0.9–1.9
Drowsy/unconscious	6	5.8	4.1–8.1	7.0	4.9–9.9
Agitated	4	2.9	1.9–4.3	2.9	1.8–4.6
Lethargy	15	3.1	2.4–3.9	4.0	3.0–5.2
Feeding ability reduced	13	6.6	5.1–8.7	9.4	6.9–12.8
No spontaneous movement	9	5.3	4.0–7.0	6.4	4.7–8.7
Consolability: continues to cry/fuss	4	4.2	2.7–6.7	5.2	3.2–8.3
Central cyanosis	3	10.8	6.5–17.8	12.2	7.6–19.5
Dehydration	6	1.3	0.9–1.8	1.5	1.0–2.2
Digital capillary refill 2+s	10	2.5	1.9–3.3	3.3	2.4–4.6
Skin rash	9	0.8	0.6–1.1	0.9	0.6–1.4
Umbilical discharge	5	1.0	0.6–1.5	1.1	0.6–2.0
Bulging fontanel	1	4.3	2.3–8.2	5.3	2.7–10.5
Eye discharge	---	---	---	---	---
Jaundice	---	---	---	---	---

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Resp rate < 40</td><td>18</td><td>0.9</td><td>0.7–1.2</td><td>1.1</td><td>0.8–1.6</td></tr>
<tr><td>Resp rate ≥60</td><td>22</td><td>3.8</td><td>3.0–4.6</td><td>3.8</td><td>2.9–5.0</td></tr>
<tr><td>Temp. < 35.5</td><td>2</td><td>2.4</td><td>1.2–4.7</td><td>3.4</td><td>1.7–6.8</td></tr>
<tr><td>Temp.≥ 38</td><td>15</td><td>2.7</td><td>2.2–3.4</td><td>3.4-</td><td>2.6–4.5</td></tr>
</table>
</td></tr>
<tr><td>Ronfani[99]

<u>Study type:</u>
prospective cohort study

EL: 2+</td><td><u>Country:</u>
Brazil

<u>Aim:</u>
To estimate sensitivity, specificity, and predictive value of different signs of severe bacterial infection (SBI) in neonates upon presentation to an emergency and neonatology department

<u>Setting, inclusion/exclusion</u>
All neonates (< 28 days) presenting at hospital and admitted to the emergency and neonatology department of Instituto Materno Infantil de Pernambuco from1 March 1995 to 29 Feb 1996 infants with ‘birth-related problems’ were excluded. Number not reported.

Data on age, sex, type of delivery, birthweight, gestational age, weight and length at admission, type of feeding collected at admission

Signs reported by mother/carer:
• Difficult breathing
• Fever
• Diarrhoea
• Cough
• Vomiting</td><td>They recruited 83 (42 male, 39 female) in total. SBI = 41 (49.4%); probable SBI = 9 (10.8%); other disease = 33 (39.8%)

Most common diagnosis:

Among SBI:
• pneumonia, n = 22
• sepsis, n = 10
• meningitis, n = 4
• conjunctivitis, n = 4
Among other diseases:
• jaundice, n = 9
• mild diarrhoea, n = 6
• convulsions, n = 4

Signs most frequently reported by mother/carer:
• Difficult breathing, 32%
• Diarrhoea, 26%
• Fever, 19%
• Cough, 19%
• Vomiting, 19%
• Jaundice, 16%
• Cyanosis, 14%
• Not feeding well, 11%

Signs most frequently observed by doctor:
• Severe chest indrawing, 46%
• Fast breathing (60+ breaths/minute), 40%
• Jaundice, 29%</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>
• Duration of all the above
Signs reported by doctor:
• severe chest indrawing
• Fast breathing
• Not looking well
Lab:
• Complete blood count
• CRP
• Blood culture
• Chest x-ray, CSF microscopy and culture, and urine culture only when CNS infections and UTI were suspected

<u>Designation of infection status by doctor at discharge (reference standard):</u>
• SBI, included sepsis, meningitis, severe diarrhoea, lower respiratory tract infection, UTI, severe omphalitis
• Probable SBI
• Other disease
</td><td>
• ‘Not looking well’, 25%
• pallor, 23%
• hypotonia, 22%
• cyanosis, 19%
• dehydration, 18%

Sensitivity, specificity and predictive values of best performing signs for SBI
<table>
<tr><th></th><th>PPV (%)*</th><th>Sensitivity (%)</th><th>Specificity (%)</th></tr>
<tr><td>By mothers</td><td></td><td></td><td></td></tr>
<tr><td>Difficult breathing</td><td>78</td><td>42</td><td>82</td></tr>
<tr><td>Fever</td><td>100</td><td>33</td><td>100</td></tr>
<tr><td>Diarrhoea</td><td>73</td><td>32</td><td>82</td></tr>
<tr><td>Cough</td><td>88</td><td>28</td><td>94</td></tr>
<tr><td>Vomiting</td><td>75</td><td>24</td><td>88</td></tr>
<tr><td>By doctors</td><td></td><td></td><td></td></tr>
<tr><td>S. chest indrawing</td><td>76</td><td>58</td><td>73</td></tr>
<tr><td>Fast breathing</td><td>79</td><td>52</td><td>78</td></tr>
<tr><td>Not looking well</td><td>95</td><td>40</td><td>97</td></tr>
</table>
*No negative predictive value was reported.

Fever and ‘not looking well’ were the only two signs independently associated with SBI:
Fever RR = 6.47, 95% CI 2.07 to 20.23, P< 0.001
Not looking well RR = 7.17, 95% CI 2.44 to 21.02, P< 0.001

Best sensitivity (74%) found with signs in parallel:
Doctor observed severe chest indrawing or fast breathing or ‘not looking well’ (specificity 67%, PPV 77%)
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td></td><td>6 deaths: 4 from SBI group (2 sepsis, 1 pneumonia, 1 meningitis), and 2 from ‘other disease’ group (1 severe rhesus isoimmune haemolytic disease, 1 adrenogenital syndrome)

Table :Sensitivity, specificity and predictive values of best performing signs for pneumonia
<table><tr><td></td><td>PPV (%)*</td><td>Sensitivity (%)</td><td>Specificity (%)</td></tr><tr><td>By mothers</td><td></td><td></td><td></td></tr><tr><td>Difficult breathing</td><td>63</td><td>77</td><td>84</td></tr><tr><td>Cough</td><td>88</td><td>64</td><td>97</td></tr><tr><td>Fever</td><td>56</td><td>43</td><td>89</td></tr><tr><td>By doctors</td><td></td><td></td><td></td></tr><tr><td>S. chest indrawing</td><td>45</td><td>77</td><td>66</td></tr><tr><td>Fast breathing</td><td>39</td><td>59</td><td>67</td></tr><tr><td>Not looking well</td><td>29</td><td>27</td><td>75</td></tr></table>**No negative predictive value was reported.*</td></tr>
<tr><td>Hiew[97]

<u>Study type</u>
prospective cohort study
EL:2-</td><td><u>Country:</u>
Singapore
<u>Aim:</u>
To identify the clinical features and haematological indices of bacterial infection amongst young infants and to determine retrospectively the findings significantly associated with positive bacterial cultures.
<u>Setting, inclusion/exclusion:</u>
July 1989-Febuary 1991, infants ≤3 mo with suspected bacterial infection and admitted to the</td><td>The recruited 100 infants with mean age of 46wk (SD:3.06)., 60 male & 40 female. The most common clinical features among the 100 infants are fever (n = 85), lethargy (n = 44), hepatomegaly (n = 39), poor feeding (n = 35), irritability (n = 30), splenomegaly (n = 23), skin mottling (n = 17), diarrhoea (n = 15), respiratory distress (n = 12), hypotonia (n = 12).

Table :Most common clinical features of bacterial infections in young infants. Positive/Total evaluations 30/100 (30%).
<table><tr><td>Feature</td><td>Infected (n)</td><td>Non-infected (n)</td><td>PPV (%)</td><td>Sensitivity (%)</td><td>P value</td></tr><tr><td>Respiratory distress</td><td>7</td><td>5</td><td>58</td><td>23</td><td>< 0.01</td></tr><tr><td>Cyanosis</td><td>6</td><td>5</td><td>55</td><td>20</td><td>< 0.05</td></tr><tr><td>Grunting</td><td>5</td><td>7</td><td>42</td><td>17</td><td>Ns</td></tr></table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr>
<td></td>
<td>Paediatric Department, Tan Tock Seng Hospital. Patents already on antibiotics before evaluation were excluded.

Evaluations were:

• General features
• Cardiovascular system
• Respiratory system
• Central nervous system
• Gastrointestinal system
• Skin
Lab test:

• Total white blood cell count
• Absolute neutrophil count
• Platelet count
• Immature to total neutrophil ratio (I/T ratio)
• Nitroblue Tetrazolium test (NBT)
• CRP
• ESR
• CXR
• Blood culturex2
• Urine culturex2
• CSF FEME and culture (only with suspected meningitis)
• Skin/umbilical cord culture
Designation of infection status:

Proven bacterial infection: infants with positive bacterial cultures of a pathogenic organism from the blood, CSF, urine, sputum, pustules or umbilicus.</td>
<td>
<table>
<tr><td>Slenomegaly</td><td>9</td><td>14</td><td>39</td><td>30</td><td>Ns</td></tr>
<tr><td>Hepatomegaly</td><td>15</td><td>24</td><td>38</td><td>50</td><td>Ns</td></tr>
<tr><td>Fits</td><td>4</td><td>7</td><td>36</td><td>13</td><td>Ns</td></tr>
<tr><td>Mottled skin</td><td>6</td><td>11</td><td>35</td><td>20</td><td>Ns</td></tr>
<tr><td>Hypotonia</td><td>4</td><td>8</td><td>33</td><td>13</td><td>Ns</td></tr>
<tr><td>Diarrhoea</td><td>5</td><td>10</td><td>33</td><td>17</td><td>Ns</td></tr>
<tr><td>Fever</td><td>28</td><td>57</td><td>33</td><td>93</td><td>Ns</td></tr>
<tr><td>Lethargy</td><td>13</td><td>31</td><td>30</td><td>43</td><td>Ns</td></tr>
<tr><td>Poor feeding</td><td>10</td><td>25</td><td>29</td><td>33</td><td>Ns</td></tr>
<tr><td>Irritability</td><td>7</td><td>23</td><td>23</td><td>23</td><td>Ns</td></tr>
<tr><td>Vomiting</td><td>2</td><td>10</td><td>17</td><td>7</td><td>Ns</td></tr>
</table>

Table :Haematological findings in young infants with bacterial infections Positive/Total evaluations 30/100 (30%).
<table>
<tr><th></th><th>Total +ve tests</th><th>+ve tests & +ve culture*</th><th>+ve tests & -ve culture*</th><th>PPV (%)</th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>NPV (%)</th><th>P value</th></tr>
<tr><td>Abnormal WBC</td><td>21</td><td>8</td><td>13</td><td>38</td><td>26.7</td><td>81.4</td><td>72</td><td>Ns</td></tr>
<tr><td>Absolute neutrophil counts</td><td>55</td><td>16</td><td>39</td><td>29</td><td>53</td><td>44</td><td>68</td><td>Ns</td></tr>
<tr><td>Abnormal platelet counts</td><td>5</td><td>1</td><td>4</td><td>20</td><td>3.3</td><td>94</td><td>69</td><td>Ns</td></tr>
<tr><td>Raised I/T ratio</td><td>15</td><td>4</td><td>11</td><td>26.7</td><td>13</td><td>84</td><td>69.4</td><td>Ns</td></tr>
<tr><td>Raised</td><td>13</td><td>4</td><td>9</td><td>30.8</td><td>13.3</td><td>87.1</td><td>70.1</td><td>Ns</td></tr>
</table>
</td>
</tr>
</table>

Citation/EL	Method	Results

NBT								
Raised CRP	66	25	41	37.9	83.3	41.4	85.3	< 0.01
Raised ESR	54	21	33	38.9	70	52.9	80.4	< 0.05

*: duplication in the report (both were reported as +ve tests & -ve culture), use the provided numbers to deduce the correct column title.

Table : Results of combination of some haematological tests

	Total +ve tests	+ve tests & +ve culture	PPV (%)	Sensitivity (%)	Specificity (%)	NPV (%)	*P* value
CRP& ESR	43	18	42	60	64	78	< 0.05
CRP&WBC	16	8	50	27	89	84	< 0.05
CRP& neutrophil counts	39	14	36	47	64	74	Ns
ESR& WBCl counts	15	8	53	27	90	74	< 0.05
ESR& neutrophil counts	33	13	39	43	71	75	ns
WBC & neutrophil counts	19	7	37	23	83	72	Ns

Citation/EL	Method	Results
		No report on the number of withdrawals, exclusions and drop outs. PPV is reported as positive predictive accuracy (if clinical feature is present or test abnormal, what is the probability of infection being present?)

Sub-question 8

Are there any scoring systems that use symptoms and signs in children with fever to predict the risk of serious illness? How accurate are they? *(e.g. Yale and Rochester scales, Sensitivity/specificity/PPV/NPV)*

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr>
<td>McCarthy[100]

Study type
prospective cohort study

EL:2+</td>
<td>Country:
USA
Scale:
YOS
Aim:
To identify observation items that could be used to identify reliably and validly, serious illness in children with fever.
Time:
Nov 1, 1980 to March, 1, 1981.
Setting:
Yale-New Haven Hospital Primary care Centre-Emergency Room (PCC) or in one private practice in Milford.
N:
312 consecutive febrile children with total of 557 observations.
Age:
Children ≤24 months
Baseline use of antibiotics:
Only included infants had not received antibiotics before assessment.
Baseline use of antipyretics:</td>
<td>Example of observation item and five-point scale
<table>
<tr><td>Item</td><td>Normal
1</td><td>2</td><td>Moderate
3</td><td>4</td><td>Severe
5</td></tr>
<tr><td>Reaction to parents stimulation (hold, talk to, give bottle)</td><td>Cries briefly then stop OR Content and not crying
Other data --</td><td>-</td><td>Cries off and on-
Other data --</td><td>-</td><td>Continual cry OR Hardly responds
Other data--</td></tr>
</table>
Diagnoses in 26 children with serious illness seen in PCC
<table>
<tr><td>Diagnoses</td><td>No</td><td>Abnormal test</td></tr>
<tr><td>Bacterial meningitis</td><td>2</td><td>CSF culture</td></tr>
<tr><td>Aseptic meningitis</td><td>1</td><td>CSF pleocytosis</td></tr>
<tr><td>Bacteraemia</td><td>2</td><td>Blood culture</td></tr>
<tr><td>Pneumonia</td><td>7</td><td>Chest roentgenogram</td></tr>
<tr><td>UTI</td><td>2</td><td>Urine culture</td></tr>
<tr><td>Septic arthritis</td><td>1</td><td>Joint fluid culture</td></tr>
<tr><td>Cellulites/abscess</td><td>3</td><td>Deep soft tissue culture</td></tr>
<tr><td>Bronchiolitis/hypoxia</td><td>4</td><td>Blood gas</td></tr>
<tr><td>Bronchiolitis</td><td>3</td><td>--</td></tr>
<tr><td>Dehydration</td><td>1</td><td>Serum electrolytes</td></tr>
<tr><td>Total</td><td>26</td><td></td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>Not specified

Definition of fever:

Body temp. ≥38.3 °C (101.0 °F)

BT measurement:

Type of thermometer not specified.

Evaluations:

14 areas were identified: colour, hydration, respiration, movement, eye appearance, quality of cry, reaction to parents' stimulation, reaction to observers' stimulation, state variation, response to noise, response to visual stimulation, response to social overtures, reaching or grasping for a presented object, and playing with a presented object. The scale of the 14 items was a five-point scale.

Definition of serious illness:

1) bacterial pathogens were isolated on cultures of blood, CSF, urine, stool, joint fluid, or deep soft tissue aspirate;

2) abnormalities of electrolytes, chest roentgenograms (infiltrates) blood gas (hypoxia in bronchiolitis)

Inclusion/exclusion:

Children ≤24 months with fever ≥38.3 °C (101.0 °F) were evaluated.</td><td>Stepwise multi-regression analysis to identify items predictive of serious illness*

<table>
<tr><th>Observation item</th><th>Multiple R value</th><th>Multiple R^2 (%)</th><th>R^2 change</th></tr>
<tr><td>Quality of cry</td><td>0.494</td><td>24.4</td><td></td></tr>
<tr><td>Reaction to parents' stimulation</td><td>0.549</td><td>30.1</td><td>0.057</td></tr>
<tr><td>State variation</td><td>0.587</td><td>34.4</td><td>0.043</td></tr>
<tr><td>Colour</td><td>0.609</td><td>37.1</td><td>0.027</td></tr>
<tr><td>Hydration</td><td>0.622</td><td>38.7</td><td>0.016</td></tr>
<tr><td>Response to social overtures</td><td>0.630</td><td>39.7</td><td>0.010</td></tr>
</table>
*Based on 165 patients seen by at least one attending physician in PCC.

Agreement data for 11 observation items scored in 68 children seen by same two attending physician in PCC

<table>
<tr><th>Observation item</th><th>$_{\kappa}$w (weighted kappa)</th><th>Observed agreement (%)</th><th>Change expected agreement (%)</th></tr>
<tr><td>Playing with object</td><td>0.85</td><td>95</td><td>67</td></tr>
<tr><td>Movement</td><td>0.79</td><td>94</td><td>72</td></tr>
<tr><td>Reaction to parent stimulation</td><td>0.73*</td><td>92</td><td>69</td></tr>
<tr><td>Reaction to social overtures</td><td>0.73*</td><td>90</td><td>64</td></tr>
<tr><td>Respirations</td><td>0.58</td><td>82</td><td>56</td></tr>
<tr><td>Quality of cry</td><td>0.56*</td><td>89</td><td>74</td></tr>
<tr><td>Colour</td><td>0.55*</td><td>97</td><td>93</td></tr>
<tr><td>Appearance of eyes</td><td>0.50</td><td>80</td><td>59</td></tr>
<tr><td>State variation</td><td>0.47*</td><td>95</td><td>91</td></tr>
<tr><td>Response to visual stimulation</td><td>0.37</td><td>91</td><td>85</td></tr>
<tr><td>Hydration</td><td>0.10**</td><td>88</td><td>87</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td></td><td>
* : item included in predictive model, P< 0.001
**: item included in predictive model, P< 0.05

A discriminate function analysis revealed that the six items when used together had a specificity of 88% and sensitivity of 77% for serious illness. Only 2.7% patients with a score < or = 10 had serious illness; 92.3% with a score < or = 16 had serious illness. The six-item model combined with history and physical exam have sensitivity of 92%

Predictive model: Six observation items and their scales
<table>
<tr><td>Observation item</td><td>1
normal</td><td>3
moderate impairment</td><td>5
severe impairment</td></tr>
<tr><td>Quality of cry</td><td>Strong with normal tone or
Content and not cry</td><td>Whimpering or sobbing</td><td>Weak or moaning, high-pitched, continuous cry or hardly responds</td></tr>
<tr><td>Reaction to parents' stimulation</td><td>Cries brief or no cry and content</td><td>Cries on and off</td><td>Persistent cry with little response</td></tr>
<tr><td>State variation</td><td>If awake, stays awake or if asleep, awakens quickly</td><td>Eyes close briefly when awake or awakens with prolonged stimulation</td><td>Falls to sleep or will not rouse</td></tr>
<tr><td>Colour</td><td>Pink</td><td>pale extremities or acrocyanosis</td><td>Pale or cyanotic or mottled or ashen</td></tr>
<tr><td>Hydration</td><td>Skin and eyes normal and</td><td>Skin and eyes normal and mouth slightly dry</td><td>Skin doughy or tented and dry mucous membranes and/or sunken eyes</td></tr>
<tr><td>Response (talk, smile) to social overtures</td><td>Smiles or alerts (< or = 2 mo)</td><td>Brief smile or alert (< or = 2 mo)</td><td>No smile, anxious, dull; no alerting to social overtures (< or = 2 mo)</td></tr>
</table>

The original sample of 165 patients was divided into group A (n = 77; 12 with serious illness) and B (n = 88; 14 with serious illness) by random number table as validation process.
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td></td><td>The discriminant rule derived from group A was applied to each subject to group B; and vice versa. The resulting specificity, sensitivity, and PPV were 83%, 83% and 48 respectively for group A. and 88%, 64% and 50% respectively, for group B. moreover, 88%, 77% and 56%, respectively for the full sample.</td></tr>
<tr><td>Dagan[108]

<u>Study type</u>
prospective cohort study
EL: 2+</td><td><u>Country:</u>
USA
<u>Scale:</u>
Rochester
<u>Aim:</u>
To determine prospectively whether the Rochester criteria could identify a substantial proportion of infants hospitalised for suspected sepsis as being at low risk for SBI.
<u>Time:</u>
July 1, 1982 to June 30, 1984.
<u>Setting:</u>
Strong Memorial hospital, Rochester, New York.
<u>N</u>:
233. M:F = 1.4:1 (P = 0.001)
<u>Age:</u>
Less than3 months. Ranged from 4–89 days. Mean = 38 days.
<u>Baseline use of antibiotics:</u>
Only included infants had not received antibiotics before assessment.
<u>Baseline use of antipyretics</u>:</td><td>144/233 (62%) met all inclusion criteria in the group of at low risk for SBI. Eighty-nine (38%) did not meet one or more criteria and were considered at high risk.
Criteria for inclusion of 89 infants in high-risk group
<table>
<tr><th rowspan="2">Criteria</th><th colspan="2">Infants</th></tr>
<tr><th>N</th><th>%</th></tr>
<tr><td>signs consistent with soft tissue infection</td><td>20</td><td>22</td></tr>
<tr><td>Abnormal WBC</td><td>74</td><td>83</td></tr>
<tr><td>≥ 15000/mm^3</td><td>47</td><td>53</td></tr>
<tr><td>≤ 5000/mm^3</td><td>14</td><td>16</td></tr>
<tr><td>≥ 1500 bands/mm^3</td><td>29</td><td>33</td></tr>
<tr><td>Abnormal urinalysis</td><td>4</td><td>5</td></tr>
</table>
One (0.7%) of the 144 infants in the low risk group had SBI, compared with 22 (25%) of the 89 in the high risk group (P< 0.001). None infants in the low risk group had bacteraemia, compared with 9 (10%) of the 89 in the high risk group (P< 0.001).
The NPV of no findings consistent with a soft tissue, skeletal or ear infection, normal WBC and differential counts and normal urinalysis was 99.3% for SBIs and 100% for sepsis.
There was 60% of infants with SBIs had RT> 39 °C compared with 39% of those without bacterial infection (P = 0.04).
Distribution of ages and BT on day of hospitalisation
<table>
<tr><th></th><th colspan="2">Low risk (n = 144)</th><th colspan="2">High risk (n = 89)</th><th colspan="2">SBIs (n = 23)</th></tr>
<tr><th></th><th>N</th><th>%</th><th>N</th><th>%</th><th>N</th><th>%</th></tr>
</table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr>
<td></td>
<td>Not specified

Definition of fever:

RT ≥ 38 °C.

BT measurement:

Type of thermometer not specified.

Evaluations:

Specimen for viral culture during July to Nov
• Throat swab, stool or rectal swab, CSF and blood.
Specimen for viral culture during Nov to June:
• Nasalpharyngeal/throat swab, stool or rectal swab, CSF.
During the month of Dec to May , nasal wash specimens also were examined for the presence of RSV and Influenza A.

Sepsis workout:
• Complete blood count with differential
• Urinalysis
• Blood
• CSF and urine culture
• CSF count and protein and glucose concentration.
Serious bacterial infections:

Bacteraemia, meningitis, cellulites, osteomyelitis, gastroenteritis and UTI.

Inclusion/exclusion:

All previously health, hospitalised</td>
<td>
<table>
<tr><td colspan="7">Age (days)</td></tr>
<tr><td>< 30</td><td>55</td><td>38</td><td>37</td><td>42</td><td>12</td><td>53</td></tr>
<tr><td>31–60</td><td>67</td><td>47</td><td>40</td><td>45</td><td>7</td><td>30</td></tr>
<tr><td>> 60</td><td>22</td><td>15</td><td>12</td><td>13</td><td>4</td><td>17</td></tr>
<tr><td colspan="7">Temp. (°C.)</td></tr>
<tr><td>< 38</td><td>12</td><td>8</td><td>17</td><td>20</td><td>5</td><td>22</td></tr>
<tr><td>38–39</td><td>72</td><td>50</td><td>36</td><td>40</td><td>4</td><td>12</td></tr>
<tr><td>> 39</td><td>60</td><td>42</td><td>36</td><td>40</td><td>14</td><td>61</td></tr>
</table>

Signs and symptoms not used to discriminate between risk categories (irritability, lethargy, anorexia, diarrhoea/vomiting, URI, LRI, +ve CXR and CSF pleocytosis) occurred at similar frequencies in the low-risk, high-risk groups and those with SBIs (P> 0.05 for each assign and symptom).

Abnormal WBC as a predictor of SBIs
<table>
<tr><th></th><th>Infant with findings</th><th>SBI</th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>PPV (%)</th></tr>
<tr><td>All infants</td><td>233</td><td>23</td><td>100</td><td>10</td><td>10</td></tr>
<tr><td>Abnormal WBC</td><td>74</td><td>16</td><td>70</td><td>72</td><td>22</td></tr>
<tr><td>≥ 15000/mm^3</td><td>14</td><td>3</td><td>13</td><td>95</td><td>21</td></tr>
<tr><td>≤ 5000/mm^3</td><td>47</td><td>12</td><td>52</td><td>84</td><td>26</td></tr>
<tr><td>≥ 1500 bands/mm^3</td><td>29</td><td>8</td><td>35</td><td>90</td><td>28</td></tr>
<tr><td>More than one WBC abnormality</td><td>24</td><td>6</td><td>26</td><td>91</td><td>25</td></tr>
</table>
No single abnormality nor any combination of abnormalities adequately (not defined) predicted which infants would have SBI.

Distribution of infants with and without SBI</td>
</tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>infants < 3 months, who house officers decided to evaluate for sepsis were included.

About 10% of infants hospitalised for suspected sepsis were not enrolled because they were not considered ‘ previously healthy’.

‘Previously health’ included infants who were born at term, had no perinatal complications, had no previous or underlying disease, and had not received antibiotics before assessment.

Infants admitted for suspected sepsis with RT < 38 °C had one or more of the following: moderate to severe irritability, lethargy, vomiting, diarrhoea, dehydration, hypothermia, seizures, dyspnoea, apnoea or signs consistent with soft tissue infection.

<u>Low risk of SBIs:</u>

If infants had no findings consistent with a soft tissue, skeletal or ear infection, normal WBC and differential counts and normal urinalysis.</td><td>
<table>
<tr><td></td><td colspan="2">With SBI (n = 23)</td><td colspan="2">Without SBI (n = 210)</td><td></td></tr>
<tr><td></td><td>N</td><td>%</td><td>N</td><td>%</td><td>P</td></tr>
<tr><td>Age ≤30 days</td><td>12</td><td>53</td><td>80</td><td>38</td><td>0.19</td></tr>
<tr><td>Male</td><td>17</td><td>74</td><td>119</td><td>57</td><td>0.11</td></tr>
<tr><td>Temp. > 39 °C</td><td>14</td><td>61</td><td>82</td><td>39</td><td>0.04</td></tr>
<tr><td>Abnormal WBC</td><td>16</td><td>70</td><td>58</td><td>28</td><td>< 0.01</td></tr>
</table>
</td></tr>
<tr><td>Dagan[164]

<u>Study type</u>

prospective cohort</td><td><u>Country:</u>

Israel

<u>Aim:</u>

If febrile infants younger than 2 months of age who were defined</td><td>144/233 (62%) met all inclusion criteria in the group of at low risk for SBI. Eighty-nine (38%) did not meet one or more criteria and were considered at high risk.

One (0.7%) of the 144 infants in the low risk group had SBI, compared with 22 (25%) of the 89 in the high risk group (P< 0.001). None infants in the low risk group had bacteraemia, compared with 9 (10%) of the 89 in the high risk group (P< 0.001).</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td>study

EL: 2+</td><td>as being at low risk for having bacterial infection could be observed as outpatients without the usual complete evaluation for sepsis and without antibiotic treatment.

<u>Method:</u>

All previously healthy febrile infants were seen at the Pediatric Emergency Room over 17 .5 months were recruited.</td><td>
There was 60% of infants with SBIs had RT> 39 °C compared with 39% of those without bacterial infection (P = 0.04).

Distribution of ages and BT on day of hospitalisation

<table>
<tr><td></td><td colspan="2">Low risk (n = 144)</td><td colspan="2">High risk (n = 89)</td><td colspan="2">SBIs (n = 23)</td></tr>
<tr><td></td><td>N</td><td>%</td><td>N</td><td>%</td><td>N</td><td>%</td></tr>
<tr><td colspan="7">Age (days)</td></tr>
<tr><td>< 30</td><td>55</td><td>38</td><td>37</td><td>42</td><td>12</td><td>53</td></tr>
<tr><td>31–60</td><td>67</td><td>47</td><td>40</td><td>45</td><td>7</td><td>30</td></tr>
<tr><td>> 60</td><td>22</td><td>15</td><td>12</td><td>13</td><td>4</td><td>17</td></tr>
<tr><td colspan="7">Temp. (°C.)</td></tr>
<tr><td>< 38</td><td>12</td><td>8</td><td>17</td><td>20</td><td>5</td><td>22</td></tr>
<tr><td>38–39</td><td>72</td><td>50</td><td>36</td><td>40</td><td>4</td><td>12</td></tr>
<tr><td>> 39</td><td>60</td><td>42</td><td>36</td><td>40</td><td>14</td><td>61</td></tr>
</table>

Signs and symptoms not used to discriminate between risk categories (irritability, lethargy, anorexia, diarrhoea/vomiting, URI, LRI, +ve CXR and CSF pleocytosis) occurred at similar frequencies in the low-risk, high-risk groups and those with SBIs (P> 0.05 for each assign and symptom).

Abnormal WBC as a predictor of SBIs

<table>
<tr><td></td><td>Infant with findings</td><td>SBI</td><td>Sensitivity (%)</td><td>Specificity (%)</td><td>PPV (%)</td></tr>
<tr><td>All infants</td><td>233</td><td>23</td><td>100</td><td>10</td><td>10</td></tr>
<tr><td>Abnormal WBC</td><td>74</td><td>16</td><td>70</td><td>72</td><td>22</td></tr>
<tr><td>≥ 15000/mm^3</td><td>14</td><td>3</td><td>13</td><td>95</td><td>21</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>≤ 5000/mm^3</td><td>47</td><td>12</td><td>52</td><td>84</td><td>26</td></tr>
<tr><td>≥ 1500 bands/mm^3</td><td>29</td><td>8</td><td>35</td><td>90</td><td>28</td></tr>
<tr><td>More than one WBC abnormality</td><td>24</td><td>6</td><td>26</td><td>91</td><td>25</td></tr>
</table>
No single abnormality nor any combination of abnormalities adequately (not defined) predicted which infants would have SBI.

Distribution of infants with and without SBI
<table>
<tr><td></td><td colspan="2">With SBI (n = 23)</td><td colspan="2">Without SBI (n = 210)</td><td></td></tr>
<tr><td></td><td>N</td><td>%</td><td>N</td><td>%</td><td>P</td></tr>
<tr><td>Age ≤30 days</td><td>12</td><td>53</td><td>80</td><td>38</td><td>0.19</td></tr>
<tr><td>Male</td><td>17</td><td>74</td><td>119</td><td>57</td><td>0.11</td></tr>
<tr><td>Temp. > 39 °C</td><td>14</td><td>61</td><td>82</td><td>39</td><td>0.04</td></tr>
<tr><td>Abnormal WBC</td><td>16</td><td>70</td><td>58</td><td>28</td><td>< 0.01</td></tr>
</table>
</td></tr>
<tr><td>Jaskiewicz[109]

<u>Study type</u>
prospective cohort study

EL: 2+</td><td><u>Country:</u>
USA
<u>Scale:</u>
Rochester
<u>Aim:</u>
To test the hypothesis that infants unlikely to have serious bacterial infections (SBI) can be accurately identified by low risk criteria.
<u>Time:</u>
Study 1: July 1, 1987-June 30, 1992
Study 2: July 1, 1984- Nov 30, 1984
Study 3: During 1985 through 1988.</td><td>The Rochester criteria
1) Appear generally well.
2) Previously healthy
• Born at term (≥37 wk gestation).
• No perinatal antimicrobial therapy.
• Not treated for unexplained hyperbilirubinaemia.
• Not receiving anti microbial agents.
• Not been previously hospitalised.
• No chronic or underlying illness.
• Was not hospitalised longer than mother.
3) No evidence of skin, soft tissue, bone, joint or ear infection
4) Lab values
• Peripheral WBC 5.0–15.0 x 109 cells/L (5000–15,000/mm3)
• Absolute band form count ≤1.5 x 109 cells/L (≤1500/mm3)
• ≤ 10 WBC per high power field (x 40) on microscopic examination of spun urine sediment
• ≤ 5 WBC per high power field (x 40) on microscopic examination of a stool smear (if diarrhoea).</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>
<u>Setting:</u>
Study 1: Rochester General hospital.
Study 2: Strong Memorial hospital, Rochester.
Study 3: Multi-centre intervention study.
<u>N</u>:
Study 1: 978
Study 2: 79
Study 3: 74
<u>Age:</u>
Infants ≤ 60 days.
<u>Baseline use of antibiotics:</u>
Only included infants had not received antibiotics before assessment.
Of low risk infants 308 (60.3%) were initially treated with anti-microbial agents and 203 (39.7%) were not.
<u>Baseline use of antipyretics</u>:
Not specified
<u>Definition of fever:</u>
RT ≥ 38 °C.
<u>BT measurement:</u>
</td><td>
Studies in this analyses
<table>
<tr><th>Study</th><th>Years</th><th>Total</th><th>Low risk (SBI/bacteraemia)</th><th>Not low risk</th><th>Ill appearing, insufficient data*</th></tr>
<tr><td>[1]McCarthy[100]</td><td>1987 –1992</td><td>978</td><td>381 (5/2)</td><td>472</td><td>125</td></tr>
<tr><td>[2] Dagan[258]</td><td>1984</td><td>79</td><td>56 (0/0)</td><td>22</td><td>1</td></tr>
<tr><td>Total 1</td><td></td><td>1057</td><td>437 (5/2)</td><td>494</td><td>126</td></tr>
<tr><td>[3] FICSG**</td><td>1985–1988</td><td>74</td><td>74 (0/0)</td><td></td><td></td></tr>
<tr><td>Total 2</td><td></td><td></td><td>511 (5/2)</td><td></td><td></td></tr>
</table>
* :not included in analysis.
**: Febrile Infant Collaborative Study Group
The Rochester criteria had NPV 98.9% (95% CI 97.2–99.6) for SBI, and 99.5% (95% CI 98.2–99.9) for bacteraemia.
Age distribution by Risk Group
<table>
<tr><th>Age (days)</th><th colspan="2">Total (n = 1005)</th><th colspan="2">Low Risk (n = 511)*</th><th colspan="2">Not Low Risk (n = 494)</th></tr>
<tr><td></td><td>N</td><td>%</td><td>N</td><td>%</td><td>N</td><td>%</td></tr>
<tr><td>0–14</td><td>142</td><td>14.1</td><td>73</td><td>14.3</td><td>69</td><td>13.9</td></tr>
<tr><td>15–30</td><td>294</td><td>29.2</td><td>154</td><td>30.1</td><td>140</td><td>28.2</td></tr>
<tr><td>31–45</td><td>303</td><td>30.2</td><td>157</td><td>30.7</td><td>146</td><td>29.7</td></tr>
<tr><td>46–60</td><td>266</td><td>26.5</td><td>127</td><td>249</td><td>139</td><td>28.2</td></tr>
</table>
There were 1057 eligible infants with 54 infants without sufficient data. Altogether 1003 infants were evaluated, they found 72 ill appearing infants and 16 of them (22.2%) had SBI. They studied those infants who did not appear to be ill (n = 930). In those infants, there were 437 were classified as low risk, 5 of them (1.1%) had SBI; 494 infants were classified as not low risk and 61 of them (12.3%) had SBI (P< 0.05).
The 473 low risk group infants were analysed together with the 74 infants from FICSG (total n = 511 in the low risk group). Five of them (1.0%) had SBI. Three of the infants, aged 25, 41 and 54 days, had UTI. None of them were initially treated with
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>Type of thermometer not specified.

Evaluations:

See the Rochester criteria.

Age, sex, race, global assessment (judged to be well or ill-appearing by house officer or attending physician without reference to specific criteria and without reliability testing. Past medical history, and physical exam.

Lab test:

Details see Rochester criteria.

Stool smear in infants with diarrhoea was not done in study 2. Specimens of blood, CSF and urine (by bladder tap or catheterisation)

Urine specimens from selected low risk infants observed without antimicrobial therapy during 1989–1992 were not cultured due to physician preference.

Chest roentgenograms were performed when clinically indicated (tachypnoea, cough, focal abnormality on physical exam of lungs).

Inclusion/exclusion:

Febrile infants (RT ≥ 38 °C) ≤60 days of age were considered at low risk for SBI if they met the following criteria: 1) appear well; 2) were previously healthy; 3) have no focal infection; 4) have WBC count 5.0–15.0 x 10^9 cells/L (5000–</td><td>antimicrobial agents.

There were 494 infants who did not meet the low risk criteria 61 of them (12.3%) had SBI. The infections included UTI (n = 31), skin or soft tissue infection (n = 18), bacteraemia (n = 11), gastroenteritis (n = 4) and pneumonia (n = 1).

Global assessment

Infants who were not well appearing were managed expectantly and not included for data analysis. Of 72 ill appearing infants, the 16 SBI included 8 UTI, 3 meningitis, 2 bacteraemia, 2 mastitis and 1 gastroenteritis.

Isolation rates of bacterial pathogens in 931 study infants

<table>
<tr><td></td><td colspan="2">Total (n = 1005)</td><td colspan="2">Low Risk (n = 511)*</td><td colspan="2">Not Low Risk (n = 494)</td></tr>
<tr><td></td><td>N</td><td>%</td><td>N</td><td>%</td><td>N</td><td>%</td></tr>
<tr><td>Blood</td><td>922</td><td>99.0</td><td>13</td><td>1.4</td><td>48</td><td>5.2</td></tr>
<tr><td>CSF</td><td>902</td><td>97.0</td><td>0</td><td>0</td><td>47</td><td>5.2</td></tr>
<tr><td>Urine</td><td>694</td><td>74.5</td><td>34</td><td>4.9</td><td>108</td><td>15.6</td></tr>
<tr><td>Stool</td><td>63</td><td>6.8</td><td>4</td><td>6.3</td><td>0</td><td>0</td></tr>
<tr><td>Other</td><td>131</td><td>14.1</td><td>11</td><td>8.4</td><td>0</td><td>0</td></tr>
</table>
</td></tr>
</table>

Citation/EL	Methodology	Effect size
	15,000/mm^3), band form count ≤1.5 x 10^9 cells/L (≤1500/mm^3), ≤ 10 WBC per high power field on microscopic examination of spun urine sediment, and ≤ 5 WBC per high power field on microscopic examination of a stool smear (if diarrhoea). Well appearing infants who do not meet at least one of the low risk criteria were excluded from the low risk group, such infants were included in the analysis in the not low risk group even when all classifying data were not available. <u>Definition of SBI:</u> Bacteraemia, meningitis, osteomyelitis, suppurative arthritis, soft tissue infections (cellulites, abscess, mastitis, omphalitis), UTI, gastroenteritis, and pneumonia. Blood and CSF cultures were considered contaminated if non-pathogenic or commensal bacteria were identified (diphtheroids, alpha-haemolytic streptococcus, Staphylococcus epidermidism and non-pathogenic Neisseria species) Soft tissue infections were defined by physical exam with or without isolation of bacterial pathogen. UTI was defined as the isolation of > 10^4 cfu/ml. Bacterial pneumonia was defined as a focal infiltrate on chest	

Citation/EL	Methodology	Effect size
	roentgenogram in association with a bacterial pathogen isolated from the blood or the presence of capsular polysaccharide in the urine.	

Citation/EL	Methodology	Effect size
Garra[259] Study type prospective cohort study EL:2+	Country: USA Scale: Rochester criteria and Philadelphia protocol. Aim: To re-evaluate the Philadelphia protocol and the Rochester criteria for identifying infants at low risk for SBI in a new population. Time: Oct 1998- May 2004. Setting: Paediatric emergency department (PED) in an urban public hospital Bronx, NY. N: 302 infants were identified. Data were prospectively collected for 274 (91%). of the 259 infants with complete cultures, 60.2% were male. Age: Infant < = 56 days. The median age: 36 days (inter-quartile range[IQR]: 26–49). 78 infants aged < or = 28 days and 181 infants aged 29–56 days.	Infants were considered to have SBI if their blood, urine, cerebrospinal fluid, or stool cultures grew pathogenic bacteria. Infants were assigned to high- and low-risk groups for SBI according to the Philadelphia protocol and the Rochester criteria by a single investigator blinded to the final culture results. The test performance parameters of the Philadelphia protocol and the Rochester criteria in this population were compared with those reported from previous validation studies. The Rochester criteria • Appear generally well. • Previously healthy • Born at term (≥37 wk gestation). • No perinatal antimicrobial therapy. • Not treated for unexplained hyperbilirubinaemia. • Not receiving anti microbial agents. • Not been previously hospitalised. • No chronic or underlying illness. • Was not hospitalised longer than mother. • No evidence of skin, soft tissue, bone, joint or ear infection • Lab values • Peripheral WBC 5.0–15.0 x 109 cells/L (5000–15,000/mm3) • Absolute band form count ≤1.5 x 109 cells/L (≤1500/mm3) • ≤ 10 WBC per high power field (x 40) on microscopic examination of spun urine sediment • ≤ 5 WBC per high power field (x 40) on microscopic examination of a stool smear (if diarrhoea). Philadelphia Protocol • Infants > 28 days • Infant Observation Score (IOS) < or = 10 (range 5–30) • No recognisable bacterial infection on exam • Lab values • WBC < 5000–15,000/mm3 • Band-to-neutrophil ratio< 0.2 • WBC< 10/mm3 and few bacteria per high-power field on microscopic exam of spun urine. • WBC < 8/mm3 and a negative Germ stain in a non-bloody CSF specimen. • No evidence of a discrete infiltrate on CXR as determined by an attending physician. • Stool smear negative for blood and few or no WBC (for infants with diarrhoea). The median temp. was 101.4oF (IQT:100.9–101.4) . 65 (25%) infants had UTI, including 51 with UTI, including UTI, 5 with UTI and bacteraemia, 8 with bacteraemia alone, and 1 with bacteraemia and bacterial meningitis.

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>
Baseline use of antibiotics:

Not specified

Baseline use of antipyretics:

Not specified

Definition of fever:

RT ≥ 38.1 °C.

BT measurement:

Type of thermometer not specified.

Evaluations:

Prior to lab evaluation, the attending physician recorded an Overall Impression of Sepsis and Infant Observation Score:

Overall Impression of Sepsis: a three-item scale rating the likelihood of sepsis as strong, ambivalent, or negative.

Infant Observation Score: tone, colour, activity, cry, irritability, and state variation.

Lab test:

CBC with manual differential, blood culture, serum glucose, LP to obtain CSF for cell count, with differential, protein, glucose, Gram stain and culture. Urine was obtained by catheterisation for urinalysis
</td><td>
Cases of SBI identified as low risk according to the two criteria sets

<table>
<tr><th></th><th>Sex/Age (D)</th><th>Temp. (°F)</th><th>IOS (range 5–30)</th><th>Physician impression of Sepsis</th><th>WBC count</th><th>Neutrophils/Bands</th><th>Urine WBCs per hpf/Gram stain</th><th>CSF WBCs per hpf/Gram stain</th><th>+ Culture score</th><th>Culture/Bacteria</th></tr>
<tr><td>Philadelphia</td><td>F/29</td><td>101.0</td><td>8</td><td>-ve</td><td>10.0</td><td>26/1</td><td>< 5/-ve (bacteria)</td><td>2/-ve (bacteria)</td><td>Blood</td><td>E. faecalis</td></tr>
<tr><td>Rochester</td><td>F/41</td><td>100.9</td><td>12</td><td>-ve</td><td>9.7</td><td>68/1</td><td>< 5/-ve (bacteria)</td><td>2/-ve (bacteria)</td><td>Blood</td><td>Strep. agalactiae</td></tr>
<tr><td>Rochester</td><td>F/29</td><td>101.0</td><td>8</td><td>-ve</td><td>10.0</td><td>26/1</td><td>< 5/-ve (bacteria)</td><td>2/-ve (bacteria)</td><td>Blood</td><td>E. faecalis</td></tr>
</table>

One hundred eighty-one infants were assigned to risk groups using the Philadelphia protocol, and 259 infants using the Rochester criteria. In this population, the negative predictive value (NPV) of the Philadelphia protocol was 97.1% (95% confidence interval [95% CI] = 85.1% to 99.8%), compared with 99.7% in the original report, and the NPV of the Rochester criteria was 97.3% (95% CI = 90.5% to 99.2%), compared with a prior report of 98.9%.

Performance Parameters of the Philadelphia Protocol and Rochester Protocol for identifying infants at low risk of SBI in their original settings and in the Bronx.

<table>
<tr><td></td><td colspan="3">Philadelphia Protocol</td></tr>
<tr><td></td><td>Philadelphia</td><td>Bronx</td><td>P-value</td></tr>
<tr><td>Sensitivity</td><td>0.99 (0.92–1.00)</td><td>0.97 (0.87–1.00)</td><td>1.00</td></tr>
<tr><td>Specificity</td><td>0.42 (0.38–0.46)</td><td>0.23 (0.17–0.31)</td><td>< 0.01</td></tr>
<tr><td>PPV</td><td>0.14 (0.11–0.17)</td><td>0.26 (0.20–0.34)</td><td>0.001</td></tr>
<tr><td>NPV</td><td>1.00 (0.98–1.00)</td><td>0.97 (0.85–1.00)</td><td>0.201</td></tr>
<tr><td>RR</td><td>--</td><td>8.67</td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>and urine culture. Additional studies such as CXR, RSC rapid antigen test or stool culture were obtained at the discretion of the treating physician.

Definition of SBI:

Bacteraemia, meningitis, osteomyelitis, suppurative arthritis, soft tissue infections (cellulites, abscess, mastitis, omphalitis), UTI, gastroenteritis, and pneumonia.

Blood and CSF cultures were considered contaminated if non-pathogenic or commensal bacteria were identified (diphtheroids, alpha-haemolytic streptococcus, Staphylococcus epidermidism and non-pathogenic Neisseria species).

UTI:

The definition of UTI is slightly different between Rochester criteria and Philadelphia protocol, they analysed the data based on the respective definitions in each criteria set.

Inclusion/exclusion:

Infant ≦ 56 days with RT ≧38.0 °C.</td><td><table>
<tr><td></td><td colspan="3">Rochester Protocol</td></tr>
<tr><td></td><td>Rochester</td><td>Bronx</td><td>P-value</td></tr>
<tr><td>Sensitivity</td><td>0.92 (0.84–0.97)</td><td>0.97 (0.89–0.99)</td><td>0.44</td></tr>
<tr><td>Specificity</td><td>0.50 (0.47–0.53)</td><td>0.39 (0.33–0.47)</td><td>0.01</td></tr>
<tr><td>PPV</td><td>0.12 (0.10–0.16)</td><td>0.35 (0.28–0.43)</td><td>< 0.01</td></tr>
<tr><td>NPV</td><td>0.97 (0.91–0.99)</td><td>0.97 (0.91–0.99)</td><td>0.26</td></tr>
<tr><td>RR</td><td>4</td><td>11.67</td><td></td></tr>
</table>
95% CI in parentheses. RR; calculated from provided info.</td></tr>
<tr><td>Teach[101]</td><td>Country:</td><td>Yale observation scales</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr>
<td>Study type
prospective cohort study

EL:2+</td>
<td>USA
Scale:
Yale Observation Scale
Aim:
To assess the efficacy of the Yale Observation Scale (YOS) in detecting occult bacteraemia in febrile, ambulatory paediatric patients with no apparent signs or symptoms of severe infection and with no focal infection.
YOS scores were assigned as part of a prospective, multicenter, randomised, interventional trial of oral and intramuscular antibiotics in preventing the complications of occult bacteraemia in febrile children.
Time:
Nov 1987- may 1991.
Setting:
Pediatric emergency departments at eight urban medical centers.
N:
6611
Age:
Children 3–36 months. Mean age 14.5 ± 8.3 months, the</td>
<td>
<table>
<tr><td>Observation item</td><td>Normal = 1</td><td>Moderate impairment = 3</td><td>Severe impairment = 5</td></tr>
<tr><td>Quality of cry</td><td>Strong or none</td><td>Whimper or sob</td><td>Weak or moaning, high-pitched, continuous cry or hardly responds</td></tr>
<tr><td>Reaction to parent stimulation</td><td>Cries brief or no cry and content</td><td>Cries on and off</td><td>Persistent cry with little response</td></tr>
<tr><td>State variation</td><td>If awake, stays awake or if asleep, awakens quickly</td><td>Eyes close briefly when awake or awakens with prolonged stimulation</td><td>No arousal and falls asleep</td></tr>
<tr><td>Colour</td><td>pink</td><td>pale extremities or acrocyanosis</td><td>pale or cyanotic or mottled or ashen</td></tr>
<tr><td>Hydration</td><td>Skin and eyes normal and</td><td>Skin and eyes normal and mouth slightly dry</td><td>Skin doughy or tented and dry mucous membranes and/or sunken eyes</td></tr>
<tr><td>Response to social overtures</td><td>Smiles or alerts (consistently)</td><td>Brief smile or alert</td><td>No smile, anxious, dull; no alerting to social overtures</td></tr>
</table>

The eight centres enrolled 6680 patients who received medication and 43 were excluded from analysis because of lost of blood cultures; 23 were excluded because of incomplete YOS score, and 3 were excluded because of failure to meet enrolment criteria (n = 2) or insufficient follow-up (n = 1); 6329 (96%) had nonfocal febrile illness and 351 (4%) had otitis media.
There were 6611 assessable patients, who had both a blood culture result and a YOS score assigned. The mean temp. was 39.8±0.56 °C.
The rage of YOS score was 6–14 for patients with bacteraemia and 6–24 for patients without bacteraemia.

Efficacy of an elevated YOS score in detecting bacteraemia in 6611 infants, 3–36 months old.</td>
</tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>median 12.4 months.

<u>Baseline use of antibiotics:</u>

antibiotic therapy during the prior 48 hr were excluded.

<u>Baseline use of antipyretics</u>:

Not specified

<u>Definition of fever:</u>

RT ≥ 38.1 °C.

<u>BT measurement:</u>

Type of thermometer not specified.

<u>Evaluations:</u>

The observation items in the YOS score.

<u>Lab test:</u>

Not specified.

<u>Inclusion</u>:

Children, 3 to 36 months of age with a temperature at least 39.0 degrees C, a nonfocal, non-toxic-appearing illness (or uncomplicated otitis media in 6/8 centres), treated as outpatients. A non-focal febrile illness was defined excluding a focal, defined bacterial illness (e.g. pharyngitis, cellulites, pneumonia).</td><td>
<table>
<tr><td></td><td>With bacteraemia</td><td></td><td>Without bacteraemia</td><td></td></tr>
<tr><td>YOS score</td><td>No</td><td>%</td><td>No</td><td>%</td></tr>
<tr><td>> 6</td><td>55</td><td>28.6</td><td>1122</td><td>17.5</td></tr>
<tr><td>> 8</td><td>32</td><td>16.7</td><td>522</td><td>8.1</td></tr>
<tr><td>> 10</td><td>10</td><td>5.2</td><td>210</td><td>3.3</td></tr>
<tr><td>> 12</td><td>1</td><td>0.5</td><td>75</td><td>1.2</td></tr>
<tr><td>YOS score</td><td>Sensitivity %</td><td>Specificity %</td><td>PPV %</td><td>NPV %</td></tr>
<tr><td>> 6</td><td>28.6</td><td>82.5</td><td>4.7</td><td>97.4</td></tr>
<tr><td>> 8</td><td>16.7</td><td>91.9</td><td>5.8</td><td>97.3</td></tr>
<tr><td>> 10</td><td>5.2</td><td>96.7</td><td>4.5</td><td>97.1</td></tr>
<tr><td>> 12</td><td>0.5</td><td>98.8</td><td>1.3</td><td>97.1</td></tr>
</table>

<table>
<tr><td>YOS score</td><td>PPV %</td><td>NPV %</td><td>RR</td></tr>
<tr><td>> 6</td><td>4.7</td><td>97.4</td><td>1.81</td></tr>
<tr><td>> 8</td><td>5.8</td><td>97.3</td><td>2.15</td></tr>
<tr><td>> 10</td><td>4.5</td><td>97.1</td><td>1.55</td></tr>
<tr><td>> 12</td><td>1.3</td><td>97.1</td><td>0.45</td></tr>
</table>
RR: calculated from provided info.

The median YOS score for both patients with bacteraemia (n = 192) and patients without bacteraemia (n = 6419) was 6, but the mean rank among patients with bacteraemia was significantly higher (P < 0.0001).</td></tr>
</table>

Citation/EL	Methodology	Effect size
	Exclusion: Toxic clinical appearance, children required admission and IV antibiotic therapy, a known or suspected allergy to amoxicillin or cerftriaxone, a focal bacterial infection other than otitis media, a specific viral infection (e.g. varicella), a known immunodeficiency or underlying chronic disease, antibiotic therapy or immunisation during the prior 48 hr, or a lack of informed consent.	
Bonadio[106] Study type prospective cohort study EL: 2+	Country: USA Scale: Milwaukee Protocol (MP) Aim: To determine the predictive value of observation variables which assess clinical appearance and activity of febrile young infants in distinguishing infectious outcome. Time: Jan 1991-Jan 1992. Setting: ER in Children's Hospital of Wisconsin.	Observation variables • Level of activity spontaneous active, vigorous (1) diminished spontaneous activity (3) no spontaneous activity, or active only with painful stimulation (5) • Level of alertness fully awake, or asleep but awakens quickly, alerts fully (1) lethargic, arouses with difficulty (3) won't alert or arouse (5) • Respiratory status/effort no impairment, rigorous (1) mild-moderate respiratory compromise(tachypnoea , RR>or = 60 breaths/minute, retractions or grunting) (3) respiratory distress with inadequate effort (apnoea, respiratory failure requiring ventilator support) (5) • Muscle tone strong (1) diminished (3) weak, limp (5) • Peripheral perfusion pink, warm extremities (1) mottle, warm extremities (3) pale, shock (5)

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>N:
233
Age:
0–8 wk.
Baseline use of antibiotics:
Infants had received antibiotics within 72 hrs were excluded.
Baseline use of antipyretics:
Not specified
Definition of fever:
RT ≥ 38.1 °C or ≥ 100.4 °F.
BT measurement:
Type of thermometer not specified.
Evaluations & Lab test::
7 observation variables (level of activity, level of alertness, respiratory status/effort, peripheral perfusion, muscle tone, affect, feeding pattern) which qualify patient clinical appearance in order to determine reliability in distinguishing the infectious outcome.
Each variable was graded either 1, 3, or 5, with a higher score indicative of a greater degree of compromise. All infants received physical examination and sepsis</td><td>• Affect
smiles and/or not irritable (1)
irritable, consolable (3)
irritable, won’t console (5)
• Feeding pattern
strong suck, eager to feed (1)
feeds briefly, weak suck (3)
unable to feed (5)

The 3 outcome groups compared were 29 cases of serious bacterial infections, (+SBI; 10 with bacterial meningitis, 12 with bacteraemia, 7 with urinary tract infection), 45 cases of aseptic meningitis (AM) and 159 cases culture-negative with normal cerebrospinal fluid (CN-NCSF). The mean score for each of the 7 variables was significantly greater in the +SBI group compared with both the AM and CN-NCSF groups (P < 0.05), whereas there was no significant difference in mean score for each of the 7 variables between the AM and CN-NCSF groups. Stepwise discriminant analysis identified 3 variables that best distinguished outcome: affect; respiratory status/effort; and peripheral perfusion, which constituted the Young Infant Observation Scale

Results of Kruskal-Wallis test
<table><tr><td></td><td colspan="3">Mean sum ranks</td><td></td></tr><tr><td>Variable</td><td>+SBI</td><td>Aseptic meningitis</td><td>Culture –ve/normal CSF</td><td>P</td></tr><tr><td>1. Level of activity</td><td>149</td><td>115</td><td>112</td><td>0.023</td></tr><tr><td>2. Level of alertness</td><td>141</td><td>114</td><td>114</td><td>0.012</td></tr><tr><td>3. Respiratory status/effort</td><td>160</td><td>116</td><td>109</td><td>0.001</td></tr><tr><td>4. Muscle tone</td><td>146</td><td>116</td><td>112</td><td>0.042</td></tr><tr><td>5. Peripheral perfusion</td><td>158</td><td>113</td><td>111</td><td>0.0003</td></tr><tr><td>6. Affect</td><td>174</td><td>112</td><td>108</td><td>0.0001</td></tr><tr><td>7. Feeding pattern</td><td>156</td><td>102</td><td>114</td><td>0.002</td></tr></table>
Results of Mann-Whitney test</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr>
<td></td>
<td>evaluation (lumbar puncture, complete blood count/blood culture, urinalysis/urine culture).

Definition of SBI:

Bacterial meningitis, bacteraemia, UTI.

Definition of aseptic meningitis (AM):

CSF pleocytosis with –ve CSF culture for bacterial pathogen and culture -ve with normal CSF.

Inclusion:

Infants 0–8 wk with RT ≥ 38.1 °C or ≥ 100.4 °F recorded by care giver or at the time of triage.

Exclusion:

Infants who were culture –ve for bacterial pathogen and had received antibiotics within 72 hrs.</td>
<td>
<table>
<tr><td></td><td colspan="3">Mean sum ranks</td></tr>
<tr><td>Variable</td><td>Aseptic meningitis</td><td>Culture –ve/normal CSF</td><td>P</td></tr>
<tr><td>1. Level of activity</td><td>104.5</td><td>101.9</td><td>0.79</td></tr>
<tr><td>2. Level of alertness</td><td>102.5</td><td>102.5</td><td>0.99</td></tr>
<tr><td>3. Respiratory status/effort</td><td>107.4</td><td>101.1</td><td>0.53</td></tr>
<tr><td>4. Muscle tone</td><td>105.1</td><td>101.8</td><td>0.73</td></tr>
<tr><td>5. Peripheral perfusion</td><td>104.4</td><td>101.9</td><td>0.81</td></tr>
<tr><td>6. Affect</td><td>105.1</td><td>101.8</td><td>0.73</td></tr>
<tr><td>7. Feeding pattern</td><td>94.2</td><td>104.8</td><td>0.28</td></tr>
</table>

The mean total Young Infant Observation Scale score generated from assessing these 3 variables was significantly greater (P = 0.0001) in the +SBI, group (9) compared with both the AM (5) and CN-NCSF (5) groups. A total Young Infant Observation Scale score > or = 7 had a sensitivity of 76%, specificity of 75% and negative-predictive value of 96% for outcome of +SBI.

Discriminant function analysis of YIOS variables for two outcome groups
<table>
<tr><td>Outcome group</td><td>+SBI, no (%)</td><td>-SBI, no (%)</td></tr>
<tr><td>+SBI</td><td>22 (76)</td><td>37 (18)</td></tr>
<tr><td>-SBI*</td><td>7 (24)</td><td>167 (82)</td></tr>
</table>
-SBI: AM+ culture –ve/normal CSF.
</td>
</tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr>
<td>McCarthy[102]

Study type

prospective cohort study

EL : 2+</td>
<td>Country:

USA

Scale:

Acute Illness Observation Scales (AIOS) + Physical Exam (PE) + history.

Aim:

To determine if observational assessment performed in a systematic manner adds to the efficacy of the traditional history and physical examination in detecting serious illnesses in febrile children, and to determine the sensitivity of the combined evaluation

Time:

July 1, 1982 to March 15, 1983, 8 AM to 5 PM Monday to Friday.

Setting:

Primary Care Center-Emergency Room (PCC-ER) of the Yale-New Haven Hospital (n = 143) and a suburban private practice (n = 207).

N:

350

Age:

Infants < or = 28 months.</td>
<td>The AIOS has 6 items: quality of cry, reaction of crying to parent stimulation (comforting, holding), state variation (the transition from sleeping to wakefulness and wakefulness to sleeping), colour, hydration, and response to social overtures (smiling in the older child and alerting in the infant < 2 months). Each item has 3-point scale: 1 = normal, 3 = moderate; 5 = severe impairment.

Examples of history as suggesting serious illness (SI):

• Rapid breathing
• Wheezing
• Grunting
• Crying when moved
• Convulsion
Examples of PE as suggesting serious illness (SI):

• Nasal flaring
• Decreased breath sounds
• Intercostals retractions
• Full fontanelle
• Kernig sign
Specificity, sensitivity, PPV, NPV and r correlations of selected abnormalities on clinical evaluation for SI
<table>
<tr><td></td><td colspan="2">A. n = 143 PCC-ER ; 28 pt had SI</td><td colspan="2">B. n = 97 PCC-ER by 2 attending paediatricians; 14 pt has SI</td><td colspan="2">C. n = 207 Private Practice; 8 pt had SI</td></tr>
<tr><td></td><td>Abn Hx or Abn PE (n = 60)</td><td>Ill appearance, abn Hx or abn PE (n = 69)</td><td>Abn Hx or Abn PE (n = 60)</td><td>Ill appearance, abn Hx or abn PE (n = 69)</td><td>Abn Hx or Abn PE (n = 60)</td><td>Ill appearance, abn Hx or abn PE (n = 69)</td></tr>
<tr><td>Spec %</td><td>69</td><td>62</td><td>66</td><td>60</td><td>86</td><td>74</td></tr>
<tr><td>Sens %</td><td>86</td><td>89</td><td>86</td><td>93</td><td>50</td><td>75</td></tr>
<tr><td>PPV %</td><td>40</td><td>36</td><td>30</td><td>28</td><td>13</td><td>10</td></tr>
<tr><td>NPV %</td><td>85</td><td>96</td><td>97</td><td>98</td><td>98</td><td>99</td></tr>
<tr><td>RR</td><td>2.67</td><td>9</td><td>10</td><td>14</td><td>6.5</td><td>10</td></tr>
<tr><td>r correlation</td><td>0.46</td><td>0.55</td><td>0.35</td><td>0.48</td><td>0.24</td><td>0.35</td></tr>
</table>
</td>
</tr>
</table>

Citation/EL	Methodology	Effect size
	Baseline use of antibiotics: Not specified. Baseline use of antipyretics: Not specified Definition of fever: BT > or = 38.3 °C. BT measurement: Type of thermometer not specified. Evaluations & Lab test:: An attending paediatrician performed the observation using the previously reported Acute Illness Observation Scales (AIOS). Subsequently, the history and physical examination were done by an attending paediatrician, and findings were scored as to whether they suggested the presence of a serious illness. Definition of serious illness: 1. bacterial pathogens were isolated on cultures of blood, CSF, urine, stool, joint fluid, or deep soft tissue aspirate; 2. abnormalities of electrolytes, chest roentgenograms (infiltrates) blood gas (hypoxia in bronchiolitis)	RR: calculated from provided info. The combined AIOS, history, and physical examination had a higher sensitivity and *r* correlation for serious illness than did the traditional history and physical examination. Three children with serious illnesses, all of whom had no abnormalities on history and physical examination, were identified only by use of AIOS.

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>Inclusion/exclusion:
Consecutive patients < or = 24 months of age with temp. > or = 38.3 °C seen for evaluation of fever at the Primary Care Center-Emergency Room of the Yale-New Haven Hospital (n = 143) and a suburban private practice (n = 207).</td><td></td></tr>
<tr><td>McCarthy[103]

Study type
prospective cohort study

EL:2+</td><td>Country:
USA
Scale:
YOS.
Aim:
To study the occurrence and positive predictive value of history and physical examination findings suggestive of serious illness in ill-appearing and well-appearing febrile children
Time:
July 1, 1982-Nov 24, 1982. g
Setting:
Primary Care Center-Emergency Room (PCC-ER) of the Yale-New Haven Hospital .
N:
103</td><td>Ill-appearing patients had a significantly greater (P< 0 .001, Fisher’s exact test) occurrence of physical examination findings suggesting serious illness (14 of 22, 64%) than well-appearing children (12 of 81, 15%).

The trends for abnormal history findings in ill-appearing and well-appearing children were similar to those for abnormal physical examination findings but did not achieve statistical significance.

The results, indicating an important interaction between a febrile child’s appearance and physical examination findings, are discussed in terms of probability reasoning in clinical decision making.

Physical exam findings suggesting SI in ill-appearing children
<table>
<tr><th>No</th><th>Findings</th><th>Illness suggested</th></tr>
<tr><td>3</td><td>Tachypnoea</td><td rowspan="3">Pneumonia</td></tr>
<tr><td>1</td><td>Tachypnoea, rales, grunt</td></tr>
<tr><td>1</td><td>Tachypnoea, rales, retractions</td></tr>
<tr><td>4</td><td>Nuchal rigidity</td><td rowspan="2">Meningitis</td></tr>
<tr><td>1</td><td>Full fontanel</td></tr>
<tr><td>1</td><td>Buccal induration, erythema</td><td rowspan="2">Deep soft tissue infection</td></tr>
<tr><td>1</td><td>Leg erythema</td></tr>
<tr><td>1</td><td>Bloody diarrhoea</td><td rowspan="2">Enteric pathogen sepsis</td></tr>
<tr><td>1</td><td>Mottled, gray colour</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr>
<td></td>
<td>Age:
Infants < or = 28 months.
Baseline use of antibiotics:
Not specified.
Baseline use of antipyretics:
Not specified
Definition of fever:
BT > or = 38.3 °C.
BT measurement:
Type of thermometer not specified.
Evaluations & Lab test::
An attending paediatrician Patients were initially classified by an attending physician (A) as to whether they appeared ill (Yale Observation Scale score greater than 10) or well (scale score less than or equal to 10). The history was then taken by two attending physicians (A and B) and a resident; the physical examination was performed by attending physician B and the same resident.
Definition of serious illness:
1. bacterial pathogens were isolated on cultures of blood, CSF, urine, stool, joint fluid, or deep soft tissue</td>
<td>Physical exam findings suggesting SI in well-appearing children
<table>
<tr><th>No</th><th>Findings</th><th>Illness suggested</th></tr>
<tr><td>2</td><td>Tachypnoea, hyperpnea</td><td rowspan="8">Pneumonia</td></tr>
<tr><td>1</td><td>Tachypnoea, rales</td></tr>
<tr><td>1</td><td>Tachypnoea, retractions</td></tr>
<tr><td>1</td><td>Tachypnoea, prolonged expiration</td></tr>
<tr><td>1</td><td>Tachypnoea</td></tr>
<tr><td>1</td><td>Retractions</td></tr>
<tr><td>2</td><td>Rales</td></tr>
<tr><td>1</td><td>Ronchi</td></tr>
<tr><td>2</td><td>Full fontanel</td><td>Meningitis</td></tr>
</table>
The positive predictive values of abnormal physical examination findings for serious illness in ill-appearing (11 of 14, 79%) and well-appearing children (3 of 12, 25%) were significantly different (P = 0.02 by Fisher’s exact test).</td>
</tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>aspirate;
2. abnormalities of electrolytes, chest roentgenograms (infiltrates) blood gas
3. hypoxemia (as documented by an arterial Po2< or = 70 mm Hg) during a LRTI.
<u>Inclusion/exclusion</u>:
consecutive children aged less than or equal to 24 months with fever greater than or equal to 38.3 degrees C were evaluated.</td><td></td></tr>
<tr><td>Baker[104]

<u>Study type</u>
prospective cohort study

EL: 2+</td><td><u>Country:</u>
USA
<u>Scale:</u>
YOS
<u>Aim:</u>
To determine the usefulness of YOS
<u>Time:</u>
July 1987-July 1988
<u>Setting:</u>
Emergency Department of The Children’s Hospital of Philadelphia
<u>N</u>:</td><td>Yale observation scales
<table><tr><td>Observation item</td><td>Normal = 1</td><td>Moderate impairment = 3</td><td>Severe impairment = 5</td></tr><tr><td>Quality of cry</td><td>Strong or none</td><td>Whimper or sob</td><td>Weak or moaning, high-pitched, continuous cry or hardly responds</td></tr><tr><td>Reaction to parent stimulation</td><td>Cries brief or no cry and content</td><td>Cries on and off</td><td>Persistent cry with little response</td></tr><tr><td>State variation</td><td>If awake, stays awake or if asleep, awakens quickly</td><td>Eyes close briefly when awake or awakens with prolonged stimulation</td><td>No arousal and falls asleep</td></tr><tr><td>Colour</td><td>pink</td><td>pale extremities or acrocyanosis</td><td>pale or cyanotic or mottled or ashen</td></tr></table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>126

Age:

Infants 29–56 days. Mean age 42 days.

Baseline use of antibiotics:

Not specified.

Baseline use of antipyretics:

Not specified

Definition of fever:

RT> 38.2 degree C.

BT measurement:

Type of thermometer not specified.

Evaluations & Lab test:

Each infant was scored (1 to 5) on each of the six items in the Yale Observation Scale by an Emergency Department attending physician before history and physical examination. Individual scores were then added to yield a total score for each patient. An observation score of 10 or less was indicative of a generally well-appearing child, and a score of 16 or more represented and ill-appearing child.

Sepsis workout:</td><td>
<table>
<tr><td>Hydration</td><td>Skin and eyes normal and</td><td>Skin and eyes normal and mouth slightly dry</td><td>Skin doughy or tented and dry mucous membranes and/or sunken eyes</td></tr>
<tr><td>Response to social overtures</td><td>Smiles or alerts (consistently)</td><td>Brief smile or alert</td><td>No smile, anxious, dull; no alerting to social overtures</td></tr>
</table>

YOS*[260] of 126 febrile infants with 131 diagnoses
<table>
<tr><td></td><td></td><td colspan="3">Observation Scores</td></tr>
<tr><td>Diagnoses</td><td>N</td><td>6–11</td><td>11–15</td><td>16–25</td></tr>
<tr><td>Viral syndrome</td><td>70</td><td>55</td><td>6</td><td>9</td></tr>
<tr><td>Aseptic meningitis</td><td>18</td><td>9</td><td>5</td><td>4</td></tr>
<tr><td>Viral gastroenteritis</td><td>7</td><td>6</td><td>--</td><td>1</td></tr>
<tr><td>Bronchiolitis</td><td>6</td><td>6</td><td>--</td><td>1</td></tr>
<tr><td>UTI</td><td>5</td><td>4</td><td>--</td><td>1</td></tr>
<tr><td>Pneumonia</td><td>5</td><td>2</td><td>2</td><td>1</td></tr>
<tr><td>Otitis media</td><td>4</td><td>3</td><td>1</td><td>--</td></tr>
<tr><td>Bacterial sepsis</td><td>4</td><td>1</td><td>1</td><td>2</td></tr>
<tr><td>Bacterial meningitis and UTI</td><td>2</td><td>2</td><td>--</td><td>--</td></tr>
<tr><td>Pneumonia and infant botulism</td><td>1</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>Bronchiolitis and otitis media</td><td>1</td><td>1</td><td>--</td><td>--</td></tr>
<tr><td>Pneumonia and otitis media</td><td>1</td><td>1</td><td>--</td><td>--</td></tr>
<tr><td>Ingestion</td><td>1</td><td>--</td><td>--</td><td>1</td></tr>
</table>
* : Reported as ‘Admission Observation Scores’ by the author.
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>CBC, urinalysis, lumbar puncture, CXR, blood culture urine culture, CSF culture.

Other lab test:

Stool culture, serum electrolyte analysis and arterial blood gas.

<u>Definition of serious illness:</u>

Isolation of bacterial pathogens on culture of blood, CSF, urine, stool, or joint fluid; pneumonia; or aseptic meningitis.

<u>UTI:</u>

Isolation of > 10^3 colonies a single organism on a catheterized or suprapubic urine specimen.

<u>Aseptic meningitis:</u>

CSF pleocytosis with sterile blood and CSF culture.

<u>Pneumonia:</u>

Infiltration based on CXR.

<u>Inclusion/exclusion</u>:

All infants aged 29 to 56 days with rectal temperatures in excess of 38.2 degree C who presented to the Emergency Department</td><td>Of 126 infants enrolled, 37 (29%) had serious illness; 12 (9.5%) had culture-proven bacterial disease. Of all infants with an observation score < = 10(n = 91), 22% had serious illness. Applying the model[260] in which a score is 10 or less is considered a negative test for ill-appearance yielded a sensitivity of 46%, specificity of 80% and PPV of 49%, NPV 78%, RR = 2.27 (calculated from provided info).

Predictive values of YOS: serious illness
<table>
<tr><td></td><td colspan="2">Serious illness</td></tr>
<tr><td>Score</td><td>Present</td><td>Absent</td></tr>
<tr><td>> 10 (ill)</td><td>17</td><td>18</td></tr>
<tr><td>< = 10 (well)</td><td>20</td><td>71</td></tr>
</table>
Of all infants with an observation score > = 16 (20/126), only 45% (n = 20) had serious illness. Applying the model[260] in which a score is 16 or more is considered a positive test for ill-appearance yielded a sensitivity of 24%, specificity of 88% , PPV 11% and NPV 91%, RR = 1.22 (calculated from provided info).

Predictive values of YOS: bacterial diseases
<table>
<tr><td></td><td colspan="2">Serious illness</td></tr>
<tr><td>Score</td><td>Present</td><td>Absent</td></tr>
<tr><td>> 10 (ill)</td><td>4</td><td>31</td></tr>
<tr><td>< = 10 (well)</td><td>8</td><td>83</td></tr>
</table></td></tr>
<tr><td>Jamuna[105]</td><td>Country:

India</td><td>The AIORS score ≥ 10 had sensitivity of 100% and specificity of 41.6% PPV 6.6% and NPV 100% to detect bacteraemia.

Peak rectal tem: 99–104 °F. peripheral leukocyte counts: 6000–20000/mm^3, ESR: 1–20 mm 1st hr. four cases of bacteraemia were</td></tr>
</table>

Citation/EL	Methodology	Effect size
Study type prospective cohort study EL:2-	Aim: 1. To clinically evaluate selected group of febrile children without obvious localisation of infection for presence of bacteraemia. 2. to identify the offending organisms in sick-looking children. 3. to formulate criteria which will distinguish cases of 'occult bacteraemia' from those without bacteraemia, on the basis of clinical findings and lab results. Time: Sep 1994-March 1996 Setting: Prospective observational study in paediatric outpatient department and casualty. Baseline use of antibiotics Patients already on antibiotics were excluded. Baseline use of antipyretics: Patients already on antipyretics were excluded Inclusion: 3–36 months, temp. > 99F, no localising source of infection, no history of antibiotic administration, and duration of	detected and 4% of blood cultures yielded commensals. Urine culture was performed in 36% cases and all were sterile. In 8 cases of chest x-ray, 3 suggested of bronchopneumonia. All children with bacteraemia had temp. > 102 °F. Elevated ESR (15 mm) was reported to be 'highly sensitive and specific' to bacteraemia (statistics not given). No additional benefits were derived on combining ESR with total leukocyte count (statistics not given). The combination of ESR ≥15 mm/hr and TLC ≥15000/mm^3 had high sensitivity with a low PPV in predicting bacteraemia (statistics not given).

Citation/EL	Methodology	Effect size
	illness ≤ 4 days. All patients were assessed by acute illness observation scale (AIOS). Exclusion: Already on antibiotics and antipyretics, immunodepressed and on steroids. No: 100 Age: Ranged from 3–36 months and no further info. Evaluation: Using acute illness observation scale system (AIOS); 3 categories (normal, moderate impairment and severe impairment) on the following observations: • quality of cry • reaction to parent stimulation • state variation • colour • hydration • response to social overtures Lab tests: not specified	

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>McCarthy[260]

Study type
prospective cohort study

EL:2+</td><td>Country:
USA
Scale:

Aim:
1. To identify the history and observation variables on which the ‘instinctive’ clinical judgement (prior physical exam) of overall degree of illness of a febrile child is based.
2. To study the relative importance of each of these variables in arriving at a judgement of overall degree of illness.
3. To study inter-observer agreement in scoring these variables and overall assessment and the influence of factors and level of physician training on observer agreement.
4. To study the predictive power of judgement of overall degree of illness of more and less experienced observers in identifying children with more serious illness.</td><td>Mean temp. was 39.4 °C. Of 20 children with proven bacterial infections, 9 had pneumonia, 3 had bacteraemia, 2 had bacterial meningitis, 2 had UTI, 2 had periorbital cellulites, 1 had septic arthritis and 1 had 1 had peritonitis.

Result of house officer’s observation comparison with attending paediatrician’s instinctive judgement of overall degree of illness of febrile children by history and observation variables.
House officers’ sensitivity, specificity, PV of the scores of 5, 6, or 7 were 38%, 74%, 14% comparison with attending paediatrician’s 57%, 76%, and 20% respectively.
Attending paediatrician’s specificity, PV of the scores of 6 or 7 were 33%, 97%, 54% while house office was 24%, 94% and 31% respectively.
Site of body temp. measurement not reported.

Predictive values, sensitivity and specificity of selected overall assessment scores for bacterial illness or pneumonia
<table>
<tr><td></td><td>PPV (%)</td><td>Specificity (%)</td><td>Sensitivity (%)</td></tr>
<tr><td>Scores of 5, 6 or 7</td><td></td><td></td><td></td></tr>
<tr><td>Paediatrician</td><td>20</td><td>76</td><td>57</td></tr>
<tr><td>House officer</td><td>14</td><td>74</td><td>38</td></tr>
<tr><td>Scores of 6 or 7</td><td></td><td></td><td></td></tr>
<tr><td>Paediatrician</td><td>54</td><td>97</td><td>33</td></tr>
<tr><td>House officer</td><td>31</td><td>94</td><td>24</td></tr>
</table>
Ps: NPV not reported.</td></tr>
</table>

Citation/EL	Methodology	Effect size
	Time: August 1977 to February 1978 Setting: Paediatric clinic and Paediatric emergency room at Yale-New Haven Hospital. No: 219, and 31 exclusion. Age: Children ≤36 m. mean age 13.4 months. Baseline use of antibiotics No specified. Baseline use of antipyretics: Not specified. Definition of fever: BT ≥38.3 °C BT measurement: Type of thermometer not reported. Variables to assess children: A. History (scored form 1:fully ; 3 mild; 5 moderate and 7:severe) • Playfulness • Alertness • Consolability • Motor ability • Eating	

Citation/EL	Methodology	Effect size
	B. Observational (scored form 1:fully ; 3 mild; 5 moderate and 7:severe) • Playfulness • Alertness • Consolability • Motor ability • Eating • Colour • Respiration • Hydration C. Overall assessment (scored form 1:well ; 3 mildly ill; 5 moderately ill and 7:sick) Inclusion: Children with a fever ≥ 38.3 degrees and aged ≤ 36 months. Exclusion: Children given antipyretics or tepid water sponges.	
Bonadio[107] Study type prospective cohort study EL:2+	Country: USA Scale: Milwaukee Protocol Aim: To assess the efficacy of the Milwaukee Protocol for selecting children at low risk for serious bacterial infection to receive outpatient management	24/534 (4.5%) with serious bacterial infection (bacteraemia, n = 7; bacterial meningitis, n = 4; UTI, n = 11; bacterial enteritis, n = 2) Milwaukee Protocol had sensitivity of 95.8% (95% CI 88 to 100), specificity of 28% (95% CI 23 to 36), PPV of 5.9% (95% CI 3.6 to 8.2), and NPV of 99.3% (95% CI 98 to 100); RR: 8.43 (calculated from provided info). Children managed as 'compromised' if any of the following criteria from the Milwaukee protocol are not fulfilled; otherwise managed as 'uncompromised': 1. Physical examination with normal clinical appearance (patient is well hydrated, tolerating oral feedings, alert and active, with good muscle tone, no respiratory distress (respiratory rate < 60 breaths/minute, no grunting respirations or intercostals retractions)) and no sign of focal infection (middle ear, soft tissue, bone/joint) 2. Normal laboratory data profile (CSF WBC count < 10/mL, CBC WBC count < 15000/mL; urinalysis with ≤5 to 10

Citation/EL	Methodology	Effect size
	Time: Jun 1991 to Jun 1992 Setting: Consecutive febrile children presenting at ER of the Children's Hospital of Wisconsin N: 534 Age: 4 to 8 weeks Baseline use of antibiotics: Not specified Baseline use of antipyretics: Not specified Definition of fever: Rectal temperature ≥100.4 °F as reported by carer or ≥38.0 °C documented at triage BT measurement: Type of thermometer not reported. Evaluations: • Physical examination including assessment of vital	WBCs/HPF, dipstick negative for leukocyte esterase and nitrite, no infiltrate on chest radiograph if performed) 3. Reliable caretaker who understands instructions, has a telephone and transportation, and agrees to re-evaluation visit within 24 hours 4. No allergy to beta-lactam antibiotics 5. Private paediatrician contacted who agrees to outpatient management

Citation/EL	Methodology	Effect size
	signs, hydration status, peripheral perfusion, clinical appearance, and identifying signs of focal infection • Lab data analysis including CSF analysis and culture, complete blood count and culture, urinalysis and culture (obtained by catheter or SPA), and stool culture if diarrhoea with haematochezia was present <u>Designation of infection status:</u> • Serious bacterial infections included diagnoses of bacterial meningitis, bacteraemia, UTI (for catheter, ≥10^4 cfu/mL, single organism; for SPA, ≥10^3 cfu/mL, single organism), Salmonella enteritis, osteomyelitis and septic arthritis <u>Inclusion/Exclusion:</u> Beside age and fever, nothing specified	

3

In children with fever, what symptoms and signs or combination of symptoms and signs are predictive of the specific diseases defined as serious illnesses?

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr>
<td>Nielsen[132]

Study type :
prospective cohort study
EL: 2+</td>
<td>Country:
Denmark
Condition:
Meningococcal disease (MD)
Aim:
To establish criteria for early distinction between meningococcal disease and other conditions with similar clinical features, and to identify other causes for haemorrhagic rashes accompanied by fever.
Setting, inclusion/exclusion:
Each of the five participating paediatric departments enrolled consecutive patients for exactly 24 months, between September 1993 and June 1996. The paediatric population at risk was 203 000.
Inclusion criteria were children (> 1m and < 16 yr): (1) presence of haemorrhages in the skin, irrespective of size, detected at admission or during the stay in hospital; (2) rectal temperature above 38 °C at some time within the 24 hours before inclusion; and (3) age greater than 1 month and less than 16 years.</td>
<td>Clinical examination at inclusion
Examinations were recorded on preprinted study forms. They included information from the case history and a standardised physical examination which was repeated 6-24 hours later.
Table Diagnostic classification of the 264 patients
<table>
<tr><th>Group no.</th><th>Definition</th><th>Number</th><th>Median age (mth)</th></tr>
<tr><td>1</td><td>Meningococcal disease, confirmed</td><td>29</td><td>30</td></tr>
<tr><td>2</td><td>Meningococcal disease, probable</td><td>10</td><td>26</td></tr>
<tr><td>3</td><td>Invasive bacterial infection, excluding MD</td><td>6</td><td>14</td></tr>
<tr><td>4</td><td>Enterovirus infection</td><td>18</td><td>21</td></tr>
<tr><td>5</td><td>Adenovirus infection</td><td>11</td><td>22</td></tr>
<tr><td>6</td><td>No invasive bacterial disease*</td><td>140</td><td>27</td></tr>
<tr><td>7</td><td>Insufficient information**</td><td>50</td><td>18</td></tr>
<tr><td colspan="4">For statistical analyses, groups 1 and 2 were pooled and compared to groups 4-6, pooled. The latter group of 169 children were considered to be without invasive bacterial infection.
* Either no bacteria in cultures from blood or spinal fluid and no antibiotic treatment prior to culture; or no blood culture, but spontaneous recovery-that is, no antibiotic treatment before or during hospitalisation. **Either antibiotic treatment prior to blood culture; or no blood culture, but treated with antibiotics.</td></tr>
</table>
A total of 264 patients with fever and skin haemorrhages were included in the study. Two children died, one as a result of vasculitis of unknown aetiology, and one as a result of pneumococcal meningitis.
Table Univariate analysis of explanatory variables, obtained at inclusion, in 39 patients with meningococcal disease and</td>
</tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>There was only one exclusion criterion: if a child was admitted twice during the study period and fulfilled the inclusion criteria on both occasions, only the first admission was included in the study (there were two such children, neither of whom had MD)

<u>Evaluations:</u>

The patients were classified into seven groups:

Meningococcal disease, confirmed

Meningococcal disease, probable

Invasive bacterial infection, excluding MD

Enterovirus infection

Adenovirus infection

No invasive bacterial disease

Insufficient information

<u>Meningococcal disease</u>
Cases of MD were defined according to the recommendations used by the British health authorities, but with the following modifications: the diagnosis of probable cases demanded demonstration of meningococcal antigen or antimeningococcal antibodies as described below; and the</td><td>169 patients without invasive bacterial disease

<table>
<tr><th></th><th>Meningococcal disease</th><th>No invasive bacterial disease</th><th>Significance of difference (p value)</th></tr>
<tr><td>Explanatory variables</td><td>(n = 39)</td><td>(n = 169)</td><td></td></tr>
<tr><td>Case history prior to inclusion</td><td></td><td></td><td></td></tr>
<tr><td>Fever, median duration (h)</td><td>21</td><td>24</td><td>n.s.</td></tr>
<tr><td>Skin haemorrhages, median duration (h)</td><td>9</td><td>12</td><td>n.s</td></tr>
<tr><td>Antibiotic treatment</td><td>23%</td><td>2%</td><td><0.001</td></tr>
<tr><td>Coughing</td><td>15%</td><td>37%</td><td><0.05</td></tr>
<tr><td>Vomiting</td><td>44%</td><td>40%</td><td>n.s</td></tr>
<tr><td>Physical signs at inclusion</td><td></td><td></td><td></td></tr>
<tr><td>Median temperature (°C)</td><td>40.0</td><td>39.0</td><td><0.01</td></tr>
<tr><td>Nuchal rigidity</td><td>41%</td><td>3%</td><td><0.001</td></tr>
<tr><td>General condition, median sum of scores</td><td>6</td><td>9</td><td><0.001</td></tr>
<tr><td>Skin haemorrhages</td><td></td><td></td><td></td></tr>
<tr><td>Individuals with >20 skin haemorrhages</td><td>74%</td><td>51%</td><td><0.05</td></tr>
<tr><td>Maximum diameter >1 mm*</td><td>95%</td><td>22%</td><td><0.001</td></tr>
<tr><td>Maximum diameter >2 mm*</td><td>74%</td><td>8%</td><td><0.001</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr>
<td></td>
<td>category of "possible cases" was not used.

Confirmed case: clinical diagnosis of meningitis or septicaemia confirmed by culture of Neisseria meningitidis from blood and/or spinal fluid

Probable case: clinical diagnosis of meningitis or septicaemia without culture confirmation, but defined by a significant increase in meningococcal antibody titres (see below), or a high antibody titre in a single serum sample drawn during the second or third week after onset of disease, and/or demonstration serogroup A or C meningococcal capsular polysaccharide in the acute serum sample by counterimmunoelectrophoresis.

The completeness of patient inclusion could only be estimated for those with MD, because data from three different systems of registration were available: (1) the clinical departments' diagnostic files; (2) the national compulsory notification of bacteriologically verified and clinically suspected cases of MD; and (3) a national laboratory surveillance system including all meningococci isolated from patients with MD.</td>
<td>
<table>
<tr><td>Universal distribution</td><td>92%</td><td>40%</td><td><0.001</td></tr>
<tr><td>Skin haemorrhages of types</td><td>82%</td><td>7%</td><td><0.001</td></tr>
<tr><td>Blood tests at inclusion</td><td></td><td></td><td></td></tr>
<tr><td>Leucocytes,10^9/l, median</td><td>16.5</td><td>11.6</td><td><0.01</td></tr>
<tr><td>Neutrophil band forms,10^9/l, median</td><td>1.8</td><td>0.3</td><td><0.001</td></tr>
<tr><td>Neutrophils, segmented,10^9/l, median</td><td>10.8</td><td>5.6</td><td><0.01</td></tr>
<tr><td>Platelets,10^9/l, median</td><td>226</td><td>288</td><td><0.05</td></tr>
<tr><td>CRP, mg/l, median</td><td>109</td><td>20</td><td><0.001</td></tr>
<tr><td>APTT, % prolonged</td><td>23%</td><td>11%</td><td>N.S.</td></tr>
<tr><td colspan="4">Variables selected for logistic regression analysis are italicised.

A single lesion of this size was sufficient for this classification.

APTT, activated partial thromboplastin time; CRP, C reactive protein.</td></tr>
</table>

They identified an aetiological agent in only 28%. In a similar proportion they found a pathophysiological explanation: 23% had micropetechiae only above the nipple line, and had either coughed or vomited. Henoch-Schönlein purpura was present in 4%. In 45% they found no explanation of the skin haemorrhages. Among the 264 patients, blood culture was performed in 84%, a complete set of case history information was obtained in 69%, a complete physical examination in 86%, and a complete set of clinicopathological tests in 67%. Lumbar puncture was performed in 32%.

<u>Meningococcal disease</u> (N = 39; Groups 1 AND 2)
The completeness of patient inclusion was estimated for those with MD. Forty one children who fulfilled the inclusion criteria were identified from the registers; 39 of them were included. Two were not included as a result of an error, one of whom died.

Thus 39 patients included in the study had MD: 29 confirmed and 10 probable cases. There were no deaths. In the confirmed cases, the general condition was worse and meningitis was more common than in the probable cases, but there were no other major differences between the two groups. Nine of the 39 patients had been treated with antibiotics prior to admission. All were treated with intravenous antibiotics in hospital, although this was delayed until after the first clinical examination in five. Throat culture positive for meningococci in 5/30 of those with MD and in 3/145 of those without MD ($p < 0.01$).
</td>
</tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>Enterovirus (EV) and adenovirus (AV) infections were defined by demonstration of EV in serum, of EV or AV in throat culture, or seroconversion for EV antibodies.</td><td>Among the 10 probable cases of MD, nine showed a significant increase in MAT titre, and one had a high MAT titre in a single serum sample. In four of these 10 patients, a significant increase in antibody titre to capsular polysaccharides was also shown.

septicaemia or meningitis with other bacterial species (N=6, Group3)

One patient had pneumococcal meningitis and died. Five had septicaemia, caused by pneumococci in two, group A streptococci in one, group B streptococci in one, and Salmonella enteritidis in one. Capsular polysaccharide from H influenzae type b or Streptococcus pneumoniae was not found in any of the acute phase sera. With the exception of the patient with meningitis, the general condition of these six patients at admission was good: in five the sum of scores exceeded 6, and the skin haemorrhages were few, small, and of type A . Nevertheless, four started intravenous antibiotic treatment at the first clinical examination.

<u>Enterovirus and adenovirus infections</u> (N = 29; Groups 4 AND 5)
EV and AV were isolated from the throats of 15 and 11 patients, respectively, of 211 patients tested. Another three patients, of 93 tested, seroconverted for EV IgG antibodies. These 29 patients were considered to have had an acute viral infection as the cause of their disease, corresponding to a prevalence of 11%. Clinically, the children's general condition was good, and in the majority the skin haemorrhages were universally distributed micropetechiae. Enterovirus RNA was not detected in any of 129 serum samples tested.

<u>Insufficient information (N = 50; GROUP 7)</u>
In 50 children invasive bacterial infection could not be excluded owing to antibiotic treatment prior to admission or lack of blood culture. In 41 of them a test for bacterial antigens in the initial blood sample and/or a test for antimeningococcal antibodies in convalescent serum were performed, in all cases with negative results.

Table :Logistic regression analysis with selected explanatory clinical and laboratory variables from the previous table
<table>
<tr><th>Explanatory variable</th><th>p value</th><th>Adjusted Odds Ratio</th><th>95% CI</th></tr>
<tr><td>Skin haemorrhages, type C, D, or E</td><td>0.002</td><td>11.2</td><td>2.5 to 50.7</td></tr>
<tr><td>Universal distribution of skin haemorrhages</td><td>0.036</td><td>5.1</td><td>1.1 to 23.7</td></tr>
<tr><td>Maximum diameter of skin haemorrhages >2 mm</td><td>0.012</td><td>7.0</td><td>1.5 to 32.0</td></tr>
<tr><td>General condition, score <7</td><td>0.001</td><td>14.0</td><td>3.1 to 62.6</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Nuchal rigidity</td><td>0.040</td><td>6.9</td><td>1.1 to 44.0</td></tr>
<tr><td>Neutrophil band forms >0.5 × 10^9/l</td><td>0.002</td><td>38.3</td><td>3.8 to 385.1</td></tr>
<tr><td>CRP >68 mg/l*</td><td>0.0001</td><td>12.4</td><td>4.7 to 32.7</td></tr>
<tr><td colspan="4">The response variable is presence or absence of meningococcal disease.
The two* 68 mg/l equals 500 nmol/l. The logistic regression analysis was repeated with 136 mg/l as cut off point; the results were similar. regression analyses of the clinical and the laboratory variables were separate.</td></tr>
</table>

As the five clinical variables had odds ratios of the same approximate magnitude, they designed an index (varying from 0 to 5) which simply counts the number of the five explanatory variables which were positive. The sensitivity and false positive rates of a diagnostic algorithm based on the index, when different numbers of positive variables were used were: ≥1, 97%, 49%; ≥2, 97%, 12%; ≥3, 82%, 5%.These figures should be compared to what was actually done; 87% (34/39) and 23% in the two groups did receive intravenous antibiotics at the first clinical examination, before any laboratory results were available.
</td></tr>
<tr><td>Baker[162]

Study type :
prospective cohort study

EL:2+</td><td>Country:
USA
Condition:
Meningococcal disease
Aim:
To determine the incidence of meningococcal disease (MD) in children with fever and petechiae, the clinical predictors of MD, and the appropriate treatments.
Setting, inclusion/exclusion:
From November, 1982 to October 1981. Cincinnati Children’s Hospital Medical Centre, a primary and tertiary</td><td>They recruited 190 children in total. There were 15 children (8%) with documented invasive bacterial infection (group I), 8 with meningococcal meningitis and 7 with bacteraemia without meningitis. The median age of the group was 41 months (range: 6 months to 15 years); 5 were < 2yr.
Non-bacteraemic causes were documented for 39 patients (group II). The median age was 45 months (range: 3 months to 11 years); 8 were < 2 years.

Table :Fever and petechiae: physical exam and lab results
<table>
<tr><th></th><th>Group I (invasive bacterial disease, n = 15)</th><th>Group II (non-bacteraemic disease, n = 39)</th><th>P value</th></tr>
<tr><td>Physical exam</td><td></td><td></td><td></td></tr>
<tr><td>Ill appearance (no)</td><td>7</td><td>4</td><td>0.003</td></tr>
<tr><td>Sings of meningeal irritation (no)</td><td>5</td><td>1</td><td>0.004</td></tr>
<tr><td>Lab evaluation</td><td></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>care centre. Selection criteria included the presence of a fever or history of fever, a petechial rash detected before venepuncture or lumbar puncture, and age less than 21 years (range 3 months to 15 years and neonates were excluded.). Children with purpura fulminans, known bleeding diatheses, and neonates were excluded (not defined).

Clinical information regarding specific signs and symptoms of pharyngitis and assessment for degree of ill appearance were not systematically quantified but were available generally from the medical records of all patients. The number of petechiae were estimated using a scale of 0 to2, e.g., 0 indicated < 10 petechiae and 2 indicate generalised petechiae. The location of petechiae were divided 3 body areas: above the nipple line (including the head and upper extremities), the trunk and the lower extremities.

<u>Lab test:</u>

CBC with differential and platelet count, blood culture, serum glucose, chemical analysis and culture, urine analysis. CRX, ESR, CSF cell count, fluid glucose and protein.</td><td>
<table>
<tr><td>Peripheral WBC (mean no/µL [range])</td><td>17600 (3300–31100)</td><td>11600 (2800–30200)</td><td>0.005</td></tr>
<tr><td>Peripheral band forms (absolute no/µL [range])</td><td>3717 (0–18038)</td><td>523 (0–5943</td><td>< 0.001</td></tr>
<tr><td>CSF WBC > 7 cells/µL [No])</td><td>9</td><td>2</td><td>< 0.001</td></tr>
</table>

Of 15 patients, 6 (40%) in group A had generalised petechiae compared with 5 of 45 (11%) group II patients (P = 0.004, Fisher’s exact test).

Table :Location of petechiae
<table>
<tr><th></th><th>Group I (invasive bacterial disease, n = 15) (n; %)</th><th>Group II (non-bacteraemic disease, n = 39) (n; %)</th><th>P value
(Fisher’s exact test)</th></tr>
<tr><td>Location of petechia</td><td></td><td></td><td></td></tr>
<tr><td>Above nipple line</td><td>12 (80%)</td><td>35 (90%)</td><td>0.3</td></tr>
<tr><td>Trunk</td><td>11 (73%)</td><td>16 (41%)</td><td>0.03</td></tr>
<tr><td>Lower extremities</td><td>12 (80%)</td><td>11 (28%)</td><td>0.001</td></tr>
</table>

Table :Indicators of invasive bacterial disease
<table>
<tr><th></th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>PPV (%)</th></tr>
<tr><td>Peripheral WBC (> 15000 cells /µL)</td><td>67</td><td>85</td><td>63</td></tr>
<tr><td>Peripheral absolute bands forms (> 500 cells /µL)</td><td>80</td><td>74</td><td>55</td></tr>
<tr><td>CSF WBC > 7</td><td>53</td><td>95</td><td>80</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>Bacteria cultures of the blood, CSF, urine and throat; and viral cultures of the CSF, nasopharynx, and stool.</td><td>
<table>
<tr><td>cells/µL)</td><td></td><td></td><td></td></tr>
<tr><td>Any of above</td><td>93</td><td>62</td><td>48</td></tr>
</table>
Ps. NPV not reported.
</td></tr>
<tr><td>Wells[118]

<u>Study type:</u>
Prospective cohort study
EL:2+</td><td><u>Country:</u>
UK
<u>Condition:</u>
MD
<u>Aim:</u>
To examine a number of simple clinical features and investigations in children with a non-blanching rash to see which predict meningococcal infection.
<u>Setting, inclusion/exclusion</u>:
The authors prospectively enrolled all infants and children aged 15 years or less with a non-blanching rash who presented to our children's accident and emergency department over a 12 month period from 1 November 1998 to 31 October 1999 (either self or general practitioner referral). The department is the only one in the city of Nottingham and serves the children from a population of about 800 000 (a paediatric population of 135 000). All patients with a non-blanching rash were included. We defined petechiae as non-blanching</td><td>Over the 12 months of the study, there were 35 918 attendances to the children's accident and emergency department, of which 9239 were for a medical condition. A total of 233 (2.5%) children who presented to the department had a petechial or purpuric rash. We excluded 15 children who had a clear alternative diagnosis (11 with Henoch-Schonlein purpura, one with idiopathic thrombocytopenic purpura, one with haemolytic uraemic syndrome, one with acute leukaemia, and one with a previously recognised clotting disorder), leaving a total of 218 study children. Twenty four of the 218 children (11%) had proven meningococcal disease. A further four children had possible meningococcal disease with a non-blanching rash. Two had raised antibody titres to meningococcal outer membrane proteins with a greater than fourfold rise in convalescent titres, and one had a positive throat swab. A fourth child with a widespread purpuric rash required ventilation and inotropic support. She had received intramuscular benzylpenicillin before arrival and her blood culture, PCR, serology, and throat swabs were negative. Since the diagnosis was unproven, these children were all included in the non-meningococcal group for analysis. No child had laboratory confirmation of bacteraemia with any other bacteria. Eight children (3.7%) did not have blood cultures taken: they were not were treated with antibiotics and did not develop signs of sepsis. Six children were admitted with proven invasive meningococcal infection (five with meningitis) in the same 12 month period but did not have a non-blanching rash. Neither season nor age was useful in predicting meningococcal infection. Fifty five per cent of children with a non-blanching rash were less than 3 years old (median age 2 years) and meningococcal infection was also more common in younger children (median age 2 years). More children with a non-blanching rash were seen in the winter months (December to February) than in the other seasons (x^2; $P < 0.001$); although meningococcal disease was more common in the winter months, this was not statistically significant (x^2; $P = 0.3$). A total of 184 children (84%), including all 24 who were later proven to have meningococcal infection, were admitted to hospital for a median time of 24 hours. One child who was clinically well was admitted to hospital but discharged with no treatment: blood culture grew *N meningitidis* at 48 hours. She was well when she was recalled and repeat blood cultures prior to initiation of treatment were negative. A total of 101 children (46%) received antibiotics (96% intravenous, 4% oral). No child was sent home from the accident and emergency department and subsequently readmitted with meningococcal infection. One child died from meningococcal infection during the study period.

Children with meningococcal infection were more likely to be ill (OR: 16.7; 95% CI 5.8–47.6), to have an axillary temperature > 38.5 °C (OR:8.0; 95% CI 2.7–23.8), purpura (OR: 37.2; 95% CI 11.7–118.3), and a capillary refill time of more than 2 seconds (OR 29.4; 95% CI 9.4–92.6) than non-meningococcal children, although a substantial minority of children without meningococcal disease showed these features. Hypotension was more common in those with meningococcal disease but blood pressure was only measured in a third of all children. It is likely that these were selectively more unwell. No child with a rash confined to the distribution of the superior vena cava (head, neck, and chest above the nipple line) (74/218) had meningococcal infection.

Table : clinical features
<table>
<tr><td>Variable</td><td>Non-meningococcal</td><td>Meningococcal</td><td>Odds ratio</td></tr>
<tr><td>(% recorded)</td><td>(n = 194)</td><td>(n = 24)</td><td>(95% CI)</td></tr>
</table>
</td></tr>
</table>

Citation/EL	Methodology	Results
	spots in the skin, less than 2 mm in diameter, and known to be new in onset. The lesions were classed as purpura if they were more than 2 mm in diameter. Care was determined by the on-call paediatric medical team. A member of the paediatric medical team collected the data in the children's accident and emergency department, entering it on a standard pro forma at the time of presentation of the child. The following data were recorded: presenting symptoms and signs, including axillary temperature, blood pressure (hypotension was defined as 2 SD or more below the mean for age), capillary refill time (defined as normal if less than 2 seconds),and details of the rash (size and distribution). Children were also characterised as being either well (smiling or crying but consolable) or ill (toxic, irritable and crying inconsolably, or lethargic). The following investigations were sent: full blood count and differential white cell count, clotting studies (international normalised ratio (INR) and activated partial thromboplastin time ratio (APTTR)), C reactive protein	<table><tr><td></td><td></td><td></td><td></td></tr><tr><td>Health (100%)</td><td></td><td></td><td></td></tr><tr><td>Well</td><td>158 (97%)</td><td>5 (3%)</td><td></td></tr><tr><td>Ill</td><td>36 (65%)</td><td>19 (35%)</td><td>16.7 (5.8 to 47.6)</td></tr><tr><td>Size of rash (100%)</td><td></td><td></td><td></td></tr><tr><td>Petechiae only</td><td>171 (98%)</td><td>4 (2%)</td><td></td></tr><tr><td>Purpura too</td><td>23 (53%)</td><td>20 (47%)</td><td>37.2 (11.7 to 118.3)</td></tr><tr><td>Distribution</td><td></td><td></td><td></td></tr><tr><td>SVC only</td><td>74 (100%)</td><td>0 (0%)</td><td>0 (0 to 4%)</td></tr><tr><td>Rash beyond SVC</td><td>120 (83%)</td><td>24 (14%)</td><td></td></tr><tr><td>Temperature (100%)</td><td></td><td></td><td></td></tr><tr><td>Normal (< 37.5 °C)</td><td>106 (95%)</td><td>5 (5%)</td><td></td></tr><tr><td>37.5–38.5 °C</td><td>51 (91%)</td><td>5 (9%)</td><td>2.1 (0.58 to 7.5)</td></tr><tr><td>> 38.5 °C</td><td>37 (73%)</td><td>14 (27%)</td><td>8.0 (2.7 to 23.8)</td></tr><tr><td>Blood pressure (39%)</td><td></td><td></td><td></td></tr><tr><td>Normal</td><td>66 (84%)</td><td>13 (16%)</td><td></td></tr><tr><td>Hypotension</td><td>2 (29%)</td><td>5 (71%)</td><td>12.7 (2.2 to 72.5)</td></tr><tr><td>Capillary refill time (99.5%)</td><td></td><td></td><td></td></tr><tr><td>Less than 2 seconds</td><td>165 (98%)</td><td>4 (2%)</td><td></td></tr><tr><td>Over 2 seconds</td><td>28 (58%)</td><td>20 (42%)</td><td>29.4 (9.4 to 92.6)</td></tr><tr><td colspan="4">SVC, superior vena cava.</td></tr></table> Children with meningococcal infection were more likely to have an abnormal neutrophil count (OR:2.7; 95% CI 1.1–6.5) and a prolonged INR (OR:30.0; 95% CI 9.9–91.0). However, a substantial minority of children without meningococcal disease also showed these features. No child with a CRP of less than 6 mg/l (90/183) had meningococcal infection.

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>(CRP), blood culture, and polymerase chain reaction (PCR) for meningococcal DNA. Cerebrospinal fluid (CSF) was sent for microscopy, bacterial and viral culture, PCR, glucose, and protein when a lumbar puncture was clinically indicated. Pro formas were completed at the time for 197 patients; 21 (9.8%) were completed retrospectively from the case notes after patients were identified by cross checking during or at the end of the study period. Meningococcal infection was defined using the PHLS Communicable Disease Surveillance Centre enhanced surveillance for meningococcal disease definition of a positive blood, CSF, or skin culture for Neisseria meningitidis, Gram negative diplococci in CSF, or positive PCR for meningococcal DNA from blood or CSF.</td><td>Table : Investigations
<table>
<tr><td>Investigation</td><td>Non-meningococcal</td><td>Meningococcal</td><td>Odds ratio</td></tr>
<tr><td>(% done)</td><td>(n = 194)</td><td>(n = 24)</td><td>(95% CI)</td></tr>
<tr><td>Total white cell count (×10^9/l) (97%)</td><td></td><td></td><td></td></tr>
<tr><td>Normal (4–11)</td><td>104 (91%)</td><td>10 (9%)</td><td></td></tr>
<tr><td>Abnormal</td><td>83 (86%)</td><td>14 (14%)</td><td>1.8 (0.74 to 4.2)</td></tr>
<tr><td>Neutrophils (×10^9/l) (97%)</td><td></td><td></td><td></td></tr>
<tr><td>Normal (2–7.5)</td><td>116 (93%)</td><td>9 (7%)</td><td></td></tr>
<tr><td>Abnormal</td><td>71 (83%)</td><td>15 (17%)</td><td>2.7 (1.1 to 6.5)</td></tr>
<tr><td>Platelet count (×10^9/l) (93%)</td><td></td><td></td><td></td></tr>
<tr><td>Normal (> 150)</td><td>165 (90%)</td><td>18 (10%)</td><td></td></tr>
<tr><td>Abnormal</td><td>14 (70%)</td><td>6 (30%)</td><td>3.9 (1.3 to 11.5)</td></tr>
<tr><td>INR (83%)</td><td></td><td></td><td></td></tr>
<tr><td>Normal (< 1.2)</td><td>150 (94%)</td><td>10 (6%)</td><td></td></tr>
<tr><td>Prolonged</td><td>7 (33%)</td><td>14 (67%)</td><td>30.0 (9.9 to 91.0)</td></tr>
<tr><td>APTTR (83%)</td><td></td><td></td><td></td></tr>
<tr><td>Normal (< 1.18)</td><td>156 (88%)</td><td>22 (12%)</td><td></td></tr>
<tr><td>Prolonged</td><td>1 (33%)</td><td>2 (67%)</td><td>14.2 (1.2 to 163.0)</td></tr>
<tr><td>CRP (mg/l) (84%)</td><td></td><td></td><td></td></tr>
<tr><td>< 6</td><td>90 (100%)</td><td>0 (0%)</td><td>0 (0–3%)</td></tr>
<tr><td>6–99</td><td>70 (89%)</td><td>9 (11%)</td><td></td></tr>
<tr><td>> 99</td><td>6 (43%)</td><td>8 (57%)</td><td></td></tr>
</table>
Several of the clinical features and investigations were sensitive but poorly specific, while others were more specific but insensitive as predictors of meningococcal infection. A rash confined to the distribution of the superior vena cava and a normal CRP each had a</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td></td><td>
negative predictive value of 100% but no feature had a high positive predictive value. If the data are reanalysed, classing the four suspected cases described above as having meningococcal rather than non-meningococcal disease, the 100% negative predictive value and sensitivity of a rash in the superior vena cava distribution and a normal CRP are unchanged. Purpura, delayed capillary refill, hypotension, abnormal INR, and an abnormal neutrophil count become more specific but no less sensitive as predictors of meningococcal disease.
Table : Ability of the clinical findings to predict meningococcal infection
<table>
<tr><th>Variable</th><th>Sensitivity %</th><th>Specificity %</th><th>PPV %</th><th>NPV%</th><th>Risk Ratio</th></tr>
<tr><td>Illness</td><td>79 (63–95)</td><td>81 (76–87)</td><td>35 (22–47)</td><td>97 (91–100)</td><td>11.7 (2.4- --)</td></tr>
<tr><td>Purpura</td><td>83 (68–98)</td><td>88 (84–93)</td><td>47 (32–61)</td><td>98 (92–100)</td><td>23.5 (4.0 – --)</td></tr>
<tr><td>Rash beyond SVC</td><td>100 (94–100)</td><td>38 (31–45)</td><td>17 (11–23)</td><td>100 (91–100)</td><td>--</td></tr>
<tr><td>Fever > 38.5 °C</td><td>58 (39–78)</td><td>81 (75–86)</td><td>27 (15–40)</td><td>94 (88–100)</td><td>4.50 (0.68- --)</td></tr>
<tr><td>Fever > 37.5 °C</td><td>79 (63–95)</td><td>55 (48–62)</td><td>18 (11–25)</td><td>95 (88–100)</td><td>3.60 (0.5 – --)</td></tr>
<tr><td>Hypotension</td><td>28 (7–48)</td><td>97 (93–100)</td><td>71 (38–100)</td><td>84 (75–92)</td><td>4.43 (1.52–12.5)</td></tr>
<tr><td>Capillary refill > 2 seconds</td><td>83 (68–98)</td><td>85 (81–90)</td><td>42 (28–56)</td><td>98 (92–100)</td><td>21 (3.5- --)</td></tr>
<tr><td colspan="6">95% CI in parentheses. SVC, superior vena cava.</td></tr>
</table>

Table : Ability of the investigations predict meningococcal infection
<table>
<tr><th>Variable</th><th>Sensitivity %</th><th>Specificity%</th><th>PPV %</th><th>NPV%</th><th>Relative Risk</th></tr>
<tr><td>Abnormal white count</td><td>58 (39–78)</td><td>56 (48–63)</td><td>14 (7–21)</td><td>91 (84–99)</td><td>1.56</td></tr>
<tr><td>Abnormal neutrophil count</td><td>68 (49–88)</td><td>62 (55–69)</td><td>17 (9–25)</td><td>94 (87–100)</td><td>2.83</td></tr>
<tr><td>INR > 1.2</td><td>58 (39–78)</td><td>96 (92–99)</td><td>67 (47–87)</td><td>94 (88–100)</td><td>11.2</td></tr>
<tr><td>APTTR > 1.18</td><td>9 (0–19)</td><td>99 (98–100)</td><td>67 (13–100)</td><td>88 (82–94)</td><td>5.58</td></tr>
<tr><td>Platelets < 150×10^9/l</td><td>25 (8–42)</td><td>92 (88–96)</td><td>30 (10–50)</td><td>90 (84 96)</td><td>3.00</td></tr>
<tr><td>CRP > 6 mg/l</td><td>100 (96–100)</td><td>54 (47–62)</td><td>18 (10–26)</td><td>100 (92–100)</td><td>--</td></tr>
</table>
</td></tr>
</table>

Citation/EL	Methodology	Results
Thompson[133] Study type: case series. EL: 3	Country: UK Condition: MCD Aim: To determine the frequency and time of onset of clinical features of the disease to enable clinicians to make an early diagnosis before the individual is admitted to hospital. Parents also need to be aware of the importance of early symptoms to avoid delay in seeking medical care. Setting, inclusion/exclusion: Participants came from a study originally designed to determine the clinical and health service factors associated with fatal and non-fatal outcomes from meningococcal disease in hospitals. Between Dec 1, 1997, and Feb 28, 1999, they identified children aged 0–16 years who died from meningococcal disease. They did this by using the Public Health Laboratory Service network of regional epidemiologists and consultants in communicable disease control in England, Wales, and Northern Ireland.	An expert panel without knowing the final outcome, reviewed the clinical records of all children to determine the clinical presentation (meningitis, septicaemia, or both), and any hospital complications (e.g., cardiovascular failure). A case was categorised as meningitis if the child had neck stiffness, photophobia, or other CNS signs, and as septicaemia if the child had cardiovascular shock or multi-organ failure but no signs of meningitis. Some children had features of both meningitis and septicaemia. After review, they excluded two fatal cases and 106 non-fatal cases because their diagnoses did not meet the criteria for inclusion, and excluded a further 74 fatal cases and 219 non-fatal cases because we did not get parental consent. Of the remaining 114 fatal cases and 430 non-fatal cases, completed questionnaires were returned for 103 (90%) fatal cases and 345 (80%) non-fatal cases. Of the 448 children in the study, 373 were confirmed through microbiological techniques (99 died) and 75 were probable cases (four died). Analysis of symptom frequency To better represent the frequency of clinical features that would be found in a typical sample of children with meningococcal disease, they calculated the weighted mean frequency of each clinical feature in each age group. They used published age-specific case fatality rates for meningococcal disease to weight the frequency of each clinical feature based on the following formula: *Weighted mean frequency = (mean frequency in fatal cases × age-specific case fatality rate) + (mean frequency in non-fatal cases × 1–age-specific case fatality rate).* Findings Of the 448 children with meningococcal disease, 103 died. 296 (66%) children were classified by the expert panel as having predominant septicaemia, 99 (22%) with meningitis, and 53 (12%) with features of both. In the 307 (68%) children in whom meningococcal serogrouping data were available, those in serogroup B accounted for 152 (50%) cases, serogroup C for 146 (47%), and W135 and Y serogroups collectively for 9 (3%). Children who died were more likely to have had septicaemia (84% *vs.* 61%, $P< 0{\cdot}001$) and more likely to have serogroup C disease (47% *vs.* 28%, $P< 0{\cdot}001$) than those who did not die. A total of 324 children were seen by a GP and 165 (51%) were sent to hospital from the first consultation. In most children, the disease progressed very rapidly. The median time between onset and admission to hospital was 22 h in the oldest children (aged 15–16 years) and even less in younger children (13 h in those younger than 1 year, 14 h in those aged 1–4 years, 20 h in those aged 5–14 years). 113 (25%) children had symptoms in the two weeks before the onset of meningococcal disease, most of which (in 107) were suggestive of upper or lower respiratory tract infection. Only 32 (7%) children had seen a doctor in the week before the onset of disease. The features that appeared earliest were common to many self-limiting viral illnesses seen in primary care. Fever was the first symptom to be noticed in children younger than 5 years; headache the first to be seen in those older than 5 years. 94% of children developed fever at some point and most young children were irritable. Loss of appetite, nausea, and vomiting were early features for all age groups, with many children also having upper respiratory symptoms (sore throat and coryza). These features, which are not specific to meningococcal disease, lasted for about 4 h in younger children but as long as 8 h in adolescents.

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>In addition to cases confirmed through microbiological techniques, they included as probable cases children with a purpuric rash and either meningitis or evidence of septicaemic shock, in whom alternative diagnoses had been excluded. Fatal cases were identified, and a sample of 755 non-fatal cases was drawn after matching for age group (four strata) and region

Evaluation:

Parents completed a questionnaire by post (313, 69·9%) or during a personal interview (135, 30·1%) with one of the investigators after a mean of 144 days (SD 125) for fatal cases and 139 days (331) for non-fatal cases (independent t test for difference, P = 0·72) after either admission to hospital or death before admission to hospital. Parents were asked the time of day that the initial symptoms of their child’s illness began and, using a checklist, to record the presence and time of appearance of pre-defined clinical features.

To identify the time of onset as precisely as possible, they also asked parents about any episodes of illness in the</td><td>In all age groups, the first specific clinical features were signs of sepsis—leg pain, abnormal skin colour, cold hands and feet, and, in older children, thirst. Parents of younger children also reported drowsiness and difficulty in breathing (usually described as rapid or laboured breathing) and occasionally diarrhoea, at this stage. Most sepsis symptoms occurred before the first medical contact. The first classic symptom of meningococcal disease to emerge was rash, although at onset this was sometimes non-specific and only developed into a petechial and then a large haemorrhagic rash over several hours. According to the authors, the close correspondence of the median time of onset of rash and of first medical contact is unlikely to be coincidental—the importance of non-blanching rash is the central message of most public education campaigns about meningitis.

The median time of onset of specific meningitis symptoms (neck stiffness, photophobia, bulging fontanelle) was later, around 12–15 h from onset of illness. The last signs (such as unconsciousness, delirium, or seizures) were seen at a median of 15 h in infants (under 1 year of age), and about 24 h in older children.

Table: time of onset of clinical features of meningococcal disease before hospital admission.

<table>
<tr><td></td><td colspan="2">< 1 year</td><td colspan="2">1–4 years</td><td colspan="2">5–14 years</td></tr>
<tr><td>Hours of onset</td><td>Symptoms</td><td>Median (IQR)</td><td></td><td>Median (IQR)</td><td></td><td>Median (IQR)</td></tr>
<tr><td>0–4</td><td>Fever</td><td>0 (0–6)</td><td>Fever</td><td>0(0–3)</td><td>Headache</td><td>0 (0–12)</td></tr>
<tr><td></td><td>Irritable</td><td>0 (0–7)</td><td>Irritable</td><td>2(0–10)</td><td>Nausea/vomiting</td><td>2 (0–12)</td></tr>
<tr><td></td><td>Poor feeding</td><td>1(0–9)</td><td>Nausea/vomiting</td><td>3(0–11)</td><td>Fever</td><td>3(0–13)</td></tr>
<tr><td></td><td>Nausea/vomiting</td><td>1(0–11)</td><td>Decreased appetite</td><td>3(0–13)</td><td>Abnormal skin colour</td><td>5(0–29)</td></tr>
<tr><td></td><td>Coryza</td><td>2(0–13)</td><td>Drowsy</td><td>4(0–11)</td><td>Decreased appetite</td><td>6(1–17)</td></tr>
<tr><td></td><td>Drowsy</td><td>2(0–14)</td><td>Leg pain</td><td>6 (0–13)</td><td></td><td></td></tr>
<tr><td>5–8</td><td>Diarrhoea</td><td>5 (0–9)</td><td>Headache</td><td>6 (1–17)</td><td>Thirst</td><td>6 (2–16)</td></tr>
<tr><td></td><td>Abnormal skin colour</td><td>5 (0–18)</td><td>Sore throat/coryza</td><td>7 (1–19)</td><td>Sore throat/coryza</td><td>7 (0–16)</td></tr>
<tr><td></td><td>Breathing difficulty</td><td>5 (0–19)</td><td>Breathing difficulty</td><td>7 (1–17)</td><td>Leg pain</td><td>7 (0–15)</td></tr>
<tr><td></td><td>Leg pain</td><td>7 (0–15)</td><td></td><td></td><td>General aches</td><td>7 (1–18)</td></tr>
</table>
</td></tr>
</table>

Citation/EL	Methodology	Results
	previous 2 weeks. We used telephone interviews with patients' general practitioners (GPs) in 173 cases, copies of GP clinical records in 87 cases, GP referral letters in 72 cases, and complaints made to health authorities regarding alleged malpractice in three cases to verify timings where possible. When there was a discrepancy, we used the timing from the medical record.	

	Floppy muscle tone	8 (1–19)				
	Rash	8(4–18)				
9–12	Cold hands and feet	9 (1–20)	Abnormal skin colour	9 (3–18)	Drowsy	9 (1–21)
	General aches	9 (4–22)	General aches	9 (4–18)	Irritable	12 (2–22)
			Rash	9 (6–18)	Confusion/delirium	12 (8–24)
			Seizure	9 (1–18)		
			Diarrhoea	10* (6–14)		
			Cold hands and feet	11 (2–17)		
			Confusion/delirium	11 (5–17)		
			Neck stiffness	11 (8–17)		
			Photophobia	12 (6–27)		
13–16	Photophobia		Floppy muscle tone	13 (8–20)	Cold hands and feet	13 (7–26)
	Unconsciousness				Rash	14 (8–21)
	Bulging fontanelle				Neck stiffness	15* (6–25)
	Neck stiffness					
	Seizure					
17–20	Thirst				Photophobia	17 (5–39)
21–24			Unconsciousness		Diarrhoea	22 (20–25)
					seizure	24 (9–79)
> 24					Breathing difficulty	34 (10–57)
					Unconsciousness	34 (11–52)

Citation/EL	Methodology	Results

Median and IQR rounded to nearest hour.

median times of first consultation with GP; according to age group (age < 1yr = 8 hr; 1–4 years = 10 hr; 5–14 years = 15hr).

The most common early features were cold hands and feet (35–47%), leg pain (31%–63%, excluding infants) and abnormal colour (17–21%) described as pallor or mottling. Thirst, diarrhoea, and breathing difficulty presumably also indicate sepsis but were less common.

The most common classic feature was haemorrhagic rash, but even this was seen in only 42–70% of cases. Meningism was more common in older children, being present in about half the children aged over 5 years (46–53%) with about half these children also showing photophobia. The most common late feature was confusion or delirium, also occurring in almost half the children (43–49%). Between 7% and 15% were unconscious by the time they were admitted to hospital

Table: age specific frequency of clinical features of meningococcal disease before hospital admission.

Early features	< 1yr (%)	1–4 years (%)	5–14 years (%)
Leg pain	5.1	30.6	62.4
Thirst	3.4	6.4	11.4
Diarrhoea	9.9	7.8	3.1
Abnormal skin colour	20.6	16.8	18.5
Breathing difficulty	16.2	9.7	7.1
Cold hands and feet	44.0	46.7	34.9
Classical features			
Haemorrhagic rash	42.3	64.2	69.8
Neck pain and stiffness	15.5	28.1	45.9
Photophobia	24.5	24.1	26.4
Bulging fontanelle	11.5	NA	NA
Late features			
Confusion or delirium	NA	42.8	49.4

Citation/EL	Methodology	Results

Seizure	8.9	12.8	7.8
Unconsciousness	7.0	9.1	5.9

Analyses of the proportion of children who developed specific groups of clinical features over the 36 h after the onset of illness showed that few children developed any new symptoms after 24 h after onset. The order of symptom progression in all age groups was fever followed by sepsis symptoms, and then the classic symptoms of haemorrhagic rash, impaired consciousness, and meningism. The progression of illness was slower in the oldest children (aged 15–16 years) who were the only age group in which meningism was an earlier and more frequent feature than haemorrhagic rash and impaired consciousness.

Three features of sepsis occurred earlier in the illness and were not uncommon—leg pain (median 7 h, 37%), abnormal skin colour (10 h, 18·6%), and cold hands and feet (12 h, 43·2%). Thirst (8 h), diarrhoea (9 h), and breathing difficulties (11 h) were also early symptoms, but they were seen in fewer children (7–11%).

The median time of onset of the classic meningococcal features of haemorrhagic rash, meningism, and impaired consciousness was 13–22 h. By contrast, the median time of onset of the early, non-specific symptoms was 7–12 h. The parents of three-quarters (76·1%) of children had noticed one or more of the early symptoms before hospital admission. Fewer than 10% of children presented with the classic signs of meningism or impaired consciousness without parents having previously recognised a haemorrhagic rash or early signs of sepsis. Taking into account only the three sepsis symptoms of leg pain, abnormal skin colour, and cold hands and feet, 72% of children had one or more that was first noticed at a median time of 8 h, which was 11 h sooner than the median time of 19 h from onset to hospital admission.

Table : overall frequency and time of onset of clinical features of meningococcal disease in children before admission.

	Percentage of children (95 °CI)	Median hr of onset
Clinical features present in > 50% children		
Fever	93.9% (89–98)	1
Drowsiness	81.1% (74–88)	7
Nausea or vomiting	76.4% (67–84)	4
Irritability	66.6% (57–75)	4
Haemorrhagic rash	61.0% (51–70)	13

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Poor appetite or feeding</td><td>59.9% (50–70)</td><td>5</td></tr>
<tr><td colspan="3">Clinical features present in 20–50% children</td></tr>
<tr><td>General aches</td><td>48.5% (39–58)</td><td>7</td></tr>
<tr><td>Confusion or delirium*</td><td>45.1% (36–55)</td><td>16</td></tr>
<tr><td>Cold hands and feet</td><td>43.2% (33–53)</td><td>12</td></tr>
<tr><td>Headache*</td><td>40.5% (31–50)</td><td>0</td></tr>
<tr><td>Leg pain</td><td>36.7% (28–47)</td><td>7</td></tr>
<tr><td>Neck pain and stiffness</td><td>35.0% (26–44)</td><td>13</td></tr>
<tr><td>Photophobia</td><td>27.5% (19–36)</td><td>15</td></tr>
<tr><td>Sore throat or coryza</td><td>23.6% (15–32)</td><td>5</td></tr>
<tr><td colspan="3">Clinical features present in < 20% children</td></tr>
<tr><td>Abnormal skin colour</td><td>18.6% (11–27)</td><td>10</td></tr>
<tr><td>Floppy muscle tone **</td><td>18.3% (12–26)</td><td>13</td></tr>
<tr><td>Bulging fontanelle***</td><td>11.5% (5–18)</td><td>15</td></tr>
<tr><td>Breathing difficulty</td><td>10.8% (5–18)</td><td>11</td></tr>
<tr><td>Seizure</td><td>9.8% (4–16)</td><td>17</td></tr>
<tr><td>Unconsciousness</td><td>9.5% (4–15)</td><td>22</td></tr>
<tr><td>Increased thirst</td><td>8.1% (3–14)</td><td>8</td></tr>
<tr><td>Diarrhoea</td><td>6.6% (2–12)</td><td>9</td></tr>
<tr><td colspan="3">Percentage and median hr of onset are standardised to UK case-fatality rate.
*: only children > 1yr.
**: only children < 5yr
***: only children < 1yr.</td></tr>
</table>
</td></tr>
<tr><td>Walsh-Kelly[134]</td><td><u>Country:</u>
US</td><td>During the study period, 547 children underwent lumbar puncture and 62% of them were 0–12 months. One hundred seventy-two children, aged 1 week to 17 years were diagnosed with meningitis (53 bacterial and 119 aseptic).</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr>
<td>Study type:

Prospective cohort study

EL: 2+</td>
<td>Condition:

Meningitis

Aim:

To assess the reliability of meningeal signs and other physical findings in predicting bacterial and aseptic meningitis at various ages.

Setting, inclusion/exclusion:

From August 1985- February 1988, clinical data were recorded prospectively for all children undergoing lumbar puncture after examination by one of six paediatricians in the ED of Children’s Hospital of Wisconsin.

The child’s degree of illness was classified as well, mildly ill, toxic and moribund. Mildly ill children were defined as having stable vital signs, decreased activity, or increased irritability but were responsive and consolable. Toxic children were defined as being lethargic, inconsolable, and uninterested in their environment and showing significant alterations in respiratory or heart rates or decreased peripheral perfusion. Moribund children were defined as being unarousable with poor peripheral perfusion and unstable vital signs.</td>
<td>Table : clinical variables in meningitis by age
<table>
<tr><td></td><td colspan="5">Bacterial meningitis</td><td colspan="5">Aseptic meningitis</td></tr>
<tr><td>variable</td><td>0–6 months (n = 11) (%)</td><td>7–12 mo (n = 14) (%)</td><td>13–18 months (n = 8) (%)</td><td>> 18 months (n = 20) (%)</td><td>P*</td><td>0–6 months (n = 64) (%)</td><td>7–12 mo (n = 9) (%)</td><td>13–18 months (n = 3) (%)</td><td>> 18 months (n = 43) (%)</td><td>P*</td></tr>
<tr><td>Bulging fontanel</td><td>55</td><td>33</td><td>NA</td><td>NA</td><td>NA</td><td>14</td><td>0</td><td>NA</td><td>NA</td><td>NS</td></tr>
<tr><td>Nuchal rigidity</td><td>72</td><td>71</td><td>87</td><td>95</td><td>< 0.001< 0.003</td><td>3</td><td>22</td><td>0</td><td>79</td><td>< 0.001</td></tr>
<tr><td>Kernig’s sign</td><td>18</td><td>50</td><td>50</td><td>75</td><td>NS</td><td>6</td><td>11</td><td>0</td><td>30</td><td>< 0.01</td></tr>
<tr><td>Brudzinski’s sign</td><td>36</td><td>93</td><td>62</td><td>65</td><td>< 0.02</td><td>10</td><td>56</td><td>33</td><td>42</td><td>< 0.01</td></tr>
<tr><td>One third positive**</td><td>45</td><td>93</td><td>87</td><td>95</td><td>NS</td><td>11</td><td>56</td><td>33</td><td>88</td><td>< 0.001</td></tr>
<tr><td>Toxic/moribund</td><td>45</td><td>36</td><td>50</td><td>60</td><td>NS</td><td>14</td><td>0</td><td>0</td><td>5</td><td>NS</td></tr>
<tr><td>Lethargic/comatose</td><td>73</td><td>86</td><td>75</td><td>100</td><td></td><td>48</td><td>33</td><td>33</td><td>42</td><td>NS</td></tr>
<tr><td colspan="11">*: Chi ^{2} test for trend.
**:Nuchal rigidity, Kernig’s sign or Brudzinski’s sign</td></tr>
</table>
Table : Bacterial versus aseptic meningitis
<table>
<tr><td>variable</td><td>0–12 months (n = 25) (%)</td><td>> 12 months (n = 28) (%)</td><td>P</td><td>0–12 months (n = 73) (%)</td><td>> 12 months (n = 46) (%)</td><td>P</td></tr>
<tr><td>Bulging fontanel</td><td>44</td><td>NA</td><td></td><td>12</td><td>NA</td><td></td></tr>
<tr><td>Nuchal rigidity</td><td>52</td><td>93</td><td>< 0.01</td><td>5</td><td>73</td><td>< 0.01</td></tr>
<tr><td>Kernig’s sign</td><td>36</td><td>68</td><td>< 0.05</td><td>7</td><td>28</td><td>< 0.05</td></tr>
<tr><td>Brudzinski’s sign</td><td>68</td><td>64</td><td>NS</td><td>16</td><td>41</td><td>< 0.01</td></tr>
<tr><td>One third positive**</td><td>72</td><td>93</td><td>0.01</td><td>17</td><td>85</td><td>< 0.001</td></tr>
<tr><td>Toxic/moribund</td><td>40</td><td>57</td><td>NS</td><td>12</td><td>4</td><td>NS</td></tr>
<tr><td>Lethargic/comatose</td><td>80</td><td>93</td><td>NS</td><td>46</td><td>41</td><td>NS</td></tr>
<tr><td>Shock</td><td>16</td><td>18</td><td>NS</td><td>8</td><td>0</td><td>NS</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>After the enrolment of the first 100 patients, an infant observation scale was included for children< 24 months. Nuchal rigidity was considered present if neck stiffness was noted with active and/or passive neck flexion.

A diagnosis of bacterial meningitis was made if CSF latex agglutination or Gram stain was positive or if pathogenic bacteria grew from the CSF culture. A diagnosis of aseptic meningitis was made if the CSF WBC count ≥ 10 cells/mm^3 in neonates or ≥5 cells/mm^3 in children > 1 month, in the absence of SF latex agglutination or Gram stain was negative or if no pathogenic bacteria from the CSF culture.</td><td><table><tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>
Nuchal rigidity was present in 27% of infants aged 0–6 months with bacterial meningitis versus 95% of patients 19 months or older (P = 0.0001). Three percent of infants 0 to 6 months old with aseptic meningitis had nuchal rigidity versus 79% of patients 19 months or older (P = 0.0005). Seventy-two percent of infants 12 months of age or younger with bacterial meningitis had at least one positive meningeal sign versus 17% of infants with aseptic meningitis (P = 0.0001). Eighty-five percent of children older than 12 months with meningitis had at least one positive meningeal sign, 93% with bacterial meningitis, and 82% with aseptic meningitis.</td></tr>
<tr><td>Oostenbrink[135]

<u>Study type:</u>
prospective validation study
EL:2+</td><td><u>Country:</u>
Netherlands
<u>Condition</u>
Bacterial meningitis
<u>Aim:</u>
To devise a diagnostic decision rule to improve management of children with meningeal signs, suspected of having bacterial meningitis. The decision rule aimed to guide decisions on (1) whether a lumbar puncture is</td><td>The validation population compromised 226 patients. Lumbar puncture was performed in 146 (65%) of the children; 107 children with early discharge recovered uneventfully as documented during the OPD visit or telephone call. Eleven children did not come to the follow-up clinical and could not be reached by telephone.

Table : General characteristics of the validation set<table><tr><td>Characteristic</td><td>Number</td><td>Percentage %</td></tr><tr><td>Male gender</td><td>152</td><td>67</td></tr><tr><td>Age (years)</td><td>2.2</td><td>Range:0.5–6.0</td></tr><tr><td>Fever in history</td><td>212</td><td>94</td></tr><tr><td>Vomiting in history</td><td>111</td><td>49</td></tr><tr><td>Duration of main complaint (day)</td><td>Median: 1</td><td>IQR: 1–2</td></tr></table></td></tr>
</table>

Citation/EL	Methodology	Results

necessary in children with meningeal signs, and (2) which children need hospitalisation and empirical antibiotic treatment for bacterial meningitis.

Setting, inclusion/exclusion

They assessed the validity of this rule in an external population of four (paediatric) hospitals in The Netherlands. They identified independent predictors for bacterial meningitis from patient's history, physical exam and lab tests from previous study. The decision rule included two scoring algorithms using symptoms, signs and quickly available blood and cerebrospinal fluid (CSF) laboratory tests. To evaluate the discriminative value of both algorithms, the absolute numbers of correctly diagnosed patients and the area under the receiver operator characteristic curve were estimated, and compared with the results from the original population (n = 360).

The first algorithm is a clinical score ranging from 0.5–30 (duration of main complaint, vomiting in history, fever in history, meningeal irritation, cyanosis, petechiae, disturbed consciousness and serum CRP)

Petechiae at exam	26	12
Disturbed consciousness	20	9
Cyanosis	2	1
Serum CRP (mg/l)	18	8–70
Lumbar puncture	146	65
hospitalisation	108	48
Diagnosis		
Bacterial meningitis	25	11
Other serious bacterial infection	28	12
Viral/aseptic meningitis	43	19
Other self-limiting diseases*	130	58
*: septicaemia = 2; pneumonia = 17; UTI = 9		

Children with score < 8.5 never had bacterial meningitis, while children with a score > 20 always had bacterial meningitis; sensitivity = 100%, specificity:60%, predictive values were not reported. Patients with high clinical scores > = 20 were at high risk of bacterial meningitis and the CSF score aided little in distinguishing between patients with and without bacterial meningitis.

Table : Validation of the clinical scores on derivation and validation set together (n = 586, with 21% bacterial meningitis)

Clinical score				
	0–8.4	5.5–14.9	15.0–19.9	> = 20
No of patients	205	251	60	70
Observed prevalence, n (%, 95% CI)	0 (0, 0–2)	32 (13, 9–17)	31 (52, 39–65)	61 (87, 79–95)

Table : Validation of the CSF scores on validation set

	CSF score

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>and the second algorithm yields a CSF score ranging from −5 to 5).

<u>The patients</u>

Children aged from 1 mo to 15 years, who visited the ED with meningeal signs, without pre-existing neurological disorders were eligible. The label of ‘meningeal signs’ was applied (as in the derivation study) to 1) children with a history of pain in the neck; 2) those referred by the general practitioner for meningeal signs or 3) children with meningeal irritation as assessed by the paediatrician. To ensure enrolment of all patients with ‘ meningeal signs’, they carefully checked the ED log during the study period of November 1999-May 2001.

The outcome was the presence of bacterial meningitis, defined as the presence of elevated leukocyte count (> 5 cell/µl) in CSF of a non-traumatic puncture and a positive bacterial CSF or blood culture. Elevated CSF leukocyte count with viral growth in CSF or faeces or positive viral serology was considered as viral meningitis. absence of any isolated pathogen as aseptic meningitis. data on recovery of</td><td>
<table>
<tr><td></td><td><−3.0</td><td>−3.0—1.0</td><td>−0.5–0.5</td><td>> = 1.0</td></tr>
<tr><td>No of patients</td><td>21</td><td>55</td><td>27</td><td>13</td></tr>
<tr><td>Observed prevalence, n (%, 95% CI)</td><td>0 (0, 0–16)</td><td>1 (2,0–5)</td><td>7 (26, 8–44)</td><td>13 (100,75–100)</td></tr>
</table>

The discriminative values of the clinical and CSF algorithm in this new population were similar to those in the original population. In the total population of 586 children with meningeal signs, the rule selected 205 children (35%) who did not need a lumbar puncture and 366 children who did not need empirical treatment (62%).
</td></tr>
</table>

Citation/EL	Methodology	Results
	non-hospitalised patients were collected at their control visit or telephone call within 3–7 days after first admission by one of the paediatricians or the research fellow.	
Tunkel[136] Study type: Narrative Review EL: 2-	Aim: To review the clinical presentation of patients with acute community acquired meningitis, the approaches to diagnosis and management. Condition: Bacterial meningitis Method: They searched Medline on English literature from 1980 to 1995 on acute bacterial meningitis. Result: They found five studies reported the presenting feature of bacterial meningitis.	Fever, headache, meningismus, and signs of cerebral dysfunction (confusion, delirium or declining consciousness) were found in >85% of patients who present with acute bacterial meningitis (Geisler, 1980; Tunkel, 1995). The meningismus may be subtle or obvious, be accompanied by Kernig's and/or Brudzinski's signs, although these signs are elicited in 50% adults with bacterial meningitis and their absence never rules out the diagnosis. Other clinical findings include cranial nerve palsy and focal cerebral signs (10-20% of the cases), seizures (30%) and vomiting (35%). With disease progression in acutely ill patients, signs of increased intracranial pressure (coma, hypertension, bradycardia and cranial nerve III palsy) may also develop. About 50% of patients with meningococcaemia, with or without meningitis, present with a predominant rash (located primarily on the extremities) that is typically erythematous and macular early in infection, but may quickly evolve into a petechial phase with further coalescence into a purpuric form; new petechial lesions may form during the physical exam (Tunkel, 1995). Patients with *Listeria monocytogenes* meningitis may have seizures and focal neurological deficits early in infection, and present without ataxia, cranial nerve palsies or nystagmus as a result of rhomboencephalitis, although patients with Listerial meningitis may present without focal neurological signs (Gellin, 1989). Some patients with bacterial meningitis may not present with the classical symptoms or signs. Neonates and infants often do not have meningismus, but may present with a change in affect or state or alertness, temperature instability (hypo or hyperthermia), listlessness, high-pitched crying, fretfulness, lethargy, refusal to feed, weak suck, irritability, jaundice, vomiting, diarrhoea or respiratory distress; a bulging fontanelle is seen in 1/3 of cases and usually occurs late during the course of the illness (Saez-Llorens, 1990; Geigin, 1992) The results have to be interpreted with caution that they only searched on Medline and some of the features are mixed results from both adults and children.
Riordan[119] Study type: Retrospective	Country UK Condition: Meningitis	Forty-five episodes of meningitis occurred in 44 children over the 10-year period. Six infants had been born before 37 weeks of gestation, but all been discharged from a neonatal unit before their admission with meningitis. Twenty-nine infants were directly admitted, one of whom was re-admitted, and 15 were tertiary referrals. Five children died, three of whom had neonatal meningitis. Presenting signs, symptoms and outcomes are shown in table below. The "classical" signs (neck stiffness and/ or raised anterior

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td>chart review

EL:3</td><td><u>Aim:</u>

To examine the initial clinical presentation and to determine the causative organisms and the antibiotic sensitivity.

<u>Setting, inclusion/ exclusion:</u>

Case notes of all children <3 months with positive CSF, cultures, admitted to the Liverpool Children’s Trust between January 1982 to December 1991, were reviewed. The case notes for all but three children were eventually traced, and information from previous research was available on two of them. Infections complicating myelomeningocoeles, ventricular shunts or occurring after surgery were excluded.</td><td>fontanelle) were absent in over 50% of infants in both series.

Table: presenting symptoms and signs and outcome of infants < 3months with bacterial meningitis.
<table>
<tr><td></td><td colspan="2">1949-52</td><td colspan="2">1982-91</td></tr>
<tr><td></td><td colspan="2">N=13</td><td colspan="2">N=42</td></tr>
<tr><td>Symptoms</td><td>No</td><td>%</td><td>No</td><td>%</td></tr>
<tr><td>Poor feeding</td><td>5</td><td>38</td><td>32</td><td>76*</td></tr>
<tr><td>Fever</td><td>NA</td><td>NA</td><td>29</td><td>69</td></tr>
<tr><td>Irritable</td><td>7</td><td>54</td><td>25</td><td>60</td></tr>
<tr><td>Lethargic</td><td>1</td><td>8</td><td>14</td><td>33</td></tr>
<tr><td>Vomiting</td><td>5</td><td>38</td><td>13</td><td>31</td></tr>
<tr><td></td><td colspan="2">N=13</td><td colspan="2">N=40</td></tr>
<tr><td>Signs</td><td>No</td><td>%</td><td>No</td><td>%</td></tr>
<tr><td>Temperature ≥38 °C</td><td>NA</td><td>NA</td><td>28</td><td>70</td></tr>
<tr><td>Irritable</td><td>NA</td><td>NA</td><td>28</td><td>70</td></tr>
<tr><td>Seizure day 1</td><td>NA</td><td>NA</td><td>14</td><td>35</td></tr>
<tr><td>Full fontanelle</td><td>5</td><td>38</td><td>18</td><td>45</td></tr>
<tr><td>Neck stiffness</td><td>3</td><td>23</td><td>5</td><td>13</td></tr>
<tr><td>No “classical” signs</td><td>7</td><td>56</td><td>22</td><td>55</td></tr>
<tr><td></td><td colspan="2">N=13</td><td colspan="2">N=45</td></tr>
<tr><td>Outcome</td><td>No</td><td>%</td><td>No</td><td>%</td></tr>
<tr><td>Delay in diagnosis</td><td>4</td><td>30</td><td>7</td><td>15</td></tr>
<tr><td>Deaths</td><td>4</td><td>30</td><td>5</td><td>11</td></tr>
<tr><td colspan="5">*: $p<0.05$ by chi^2 test.</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Nielsen[132]

<u>Study type:</u>
Retrospective chart review
EL: 3</td><td><u>Country:</u>
Demark
<u>Aim:</u>
to examine the ability to diagnose purulent meningitis (PM) in children in general practice
to describe symptoms and signs in children referred on suspicion of meningitis.
<u>Setting, inclusion/ exclusion</u>
All children aged <16 years who were admitted for observation for suspected meningitis to the paediatric ward of the Department of internal Medicine, Thisted Hospital, Demark, during the 7-year period from May 1980 to April 1987. They retrospectively examined all letters of referral from GPs, hospital discharge letters of all children admitted to hospital for: 1) meningitis (n=104), 2) meningismus (n=28), 3) symptoms compatible to PM (n=25): had at least one of the following symptoms: neck stiffness, Kernig’s sign or tense fontanelle, and 4) with proven PM but admitted for another diagnosis (n=3).</td><td>A total of 160 children were included (111 boys and 49 girls, median age 5 years).
Forty-four of the children suspected for PM had been seen twice prior to their referral, antibiotics had been given to 16 of these children. Immediately before admission, an additional 4 children were given high dose of parenteral penicillin on suspicion of PM.
Other diagnosis include aseptic meningitis (n=5), aseptic meningitis w. parotitis (n=10), uncomplicated parotitis (n=2), encephalitis (n=5), upper respiratory tract infection (n=45), fever of unknown origin (n=42), pneumonia (n=21), gastroenteritis (n=4), measles (n=4), UTI (n=2) and others (n=3).
Children with PM had significantly shorter durations than children without meningitis.
Table:The duration of symptoms in 143 children suspected , and 17 with PM.
<table>
<tr><td>Duration of symptoms</td><td>PM</td><td>Other diagnosis</td><td>Total</td></tr>
<tr><td>≤ 24 hr</td><td>11 (65%)</td><td>56 (39%)</td><td>67</td></tr>
<tr><td>> 24 hr</td><td>6 (35%)</td><td>87 (61%)</td><td>93</td></tr>
<tr><td>Total</td><td>17</td><td>143</td><td>160</td></tr>
<tr><td colspan="4">Chi ^{2}= 4.1, p<0.05</td></tr>
</table>
The diagnostic specificity and sensitivity were 59% and 76% for neck stiffness and 83% and 71% for Kernig’s sign.</td></tr>
</table>

Citation/EL	Methodology	Results
Lee[175] Study type : prospective cohort study EL:2+	Country: USA Condition: Bacteraemia Aim: The purposes of this article are 2-fold: (1) to determine the prevalence of occult bacteraemia in a cohort of febrile children 3 to 36 months of age after the introduction of the *Haemophilus influenzae* type b conjugate vaccine and (2) to provide data from which to assess the risk of *Streptococcus pneumoniae* bacteraemia in well-appearing young children, so that proponents of antibiotic administration to selected febrile children are able to choose optimal criteria. Setting and inclusion/exclusion: Patients treated in the ED between January 1, 1993, and December 31, 1996, were considered initially for inclusion. Subjects at risk for occult bacteraemia if they were between 3 and 36 months of age and had a triage temperature of 39.0 °C or higher recorded in the ED by rectal or tympanic measurement. Subsequently, they excluded	Of 199868 patient visits to the emergency department, 11911 children were considered to be at risk for occult bacteraemia. Children between the ages of 3 and 36 months accounted for 70142 of the patient visits (35%) to the ED. No temperature was recorded for 2193 children (3%) and these patients were excluded from the study. Of the remaining children who were 3 to 36 months of age, 15912 (23%) had a temperature of 39.0 °C. After excluding patients, as defined, 11911 patients remained who were considered at risk for occult bacteraemia. The 3 most common diagnoses were otitis media (n = 4200), fever (n = 3228), and unspecified viral infection (n = 2896). Of these 11911 patient visits to the ED, 8974 (75%) had a complete blood cell count done and 8782 (74%) had a differential cell count performed. A manual differential cell count was performed in 7471 (63%) and an automated differential cell count was completed in the remainder of patients. Blood cultures were drawn in 9465 (79%) of the patient visits. Blood cultures were less likely to be drawn when a diagnosis of otitis media was made (71% vs. 84%, *P*<.01). Of 246 blood cultures from which organisms were isolated, 149 were considered pathogens: *S pneumoniae* in 137 (92%), *Salmonella* species in 7 (5%), *N meningitidis* in 2 (1%), group A streptococci in 2 (1%), and group B streptococci in 1 (1%). *Haemophilus influenzae* type b was not isolated from the blood of any of these children. The prevalence of occult bacteraemia in this population of 9465 children 3 to 36 months of age with a temperature of 39.0 °C or higher and no obvious source of infection is 1.57% with a 95% CI of 1.32–1.83%. Of those children with positive findings on blood culture, the most common diagnoses were fever (n = 78), otitis media (n = 46), and unspecified viral infection (n = 19). Occult bacteraemia occurred in 1.55% (95% CI 1.11–1.99%) of children with otitis media compared with 1.59% (95% CI 1.28–1.89%) of children without otitis media. The risk of occult pneumococcal bacteraemia alone is 1.45% (95% CI 1.21–1.69%). Occult pneumococcal bacteraemia occurred in 1.48% (95% CI 1.05–1.92%) and 1.43% (95% CI 1.14–1.72%) of children with and without otitis media, respectively. Because there was no significant difference between the groups, patients with otitis media were included in subsequent analyses. All subsequent analyses will focus on pneumococcal bacteraemia alone. The risk of occult pneumococcal bacteraemia was significantly lower in the 3- to 6-month-old age group than in older age groups. The 3- to 6-month-old age group had an odds ratio (OR) for pneumococcal bacteraemia of 0.22 (95% CI 0.07–0.71) compared with the 12- to 24-month-old age group. The 6- to 12-month-old (OR 1.06; 95% CI 0.73–1.55) and 24- to 36-month-old (OR 0.75; 95% CI 0.46–1.23) age groups showed no significant differences in the odds ratios when compared with the 12- to 24-month-old group. When compared with the 39.0 °C to 39.4 °C temperature group, the 40.0 °C to 40.4 °C, 40.5 °C to 40.9 °C, and 41.0 °C to 42.0 °C temperature groups showed significantly higher risks for bacteraemia with ORs of 1.90 (95% CI 1.13–3.21), 2.6 (95% CI 1.5–4.5), and 3.7 (95% CI 1.9–7.3), respectively. Rates of bacteraemia also increased with increasing values of WBC, ANC, and ABC. Univariate logistic regression for each of these variables showed significant association with occult pneumococcal bacteraemia (Pearson chi^2 probability for goodness of fit > 0.99 for WBC, ANC, and ABC). Receiver-operating characteristic curves were constructed for temperature, WBC, ANC, and ABC. The measured AUCs for WBC

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>children who were (1) admitted to the hospital, transferred to another facility, or died during the visit; (2) discharged with a diagnosis of a specific viral infection (croup, bronchiolitis, varicella, Coxsackievirus, herpangina, or stomatitis); (3) diagnosed with a focal bacterial infection, other than otitis media (pneumonia, abscess, cellulitis, meningitis, sinusitis, osteomyelitis, pyelonephritis, lymphadenitis, cholangitis, mastoiditis, impetigo, scarlet fever, streptococcal pharyngitis, or urinary tract infection); (4) known to have a chronic illness or known immunodeficiency that would alter the approach to febrile illness such as leukaemia, agranulocytosis, aplastic anaemia, arteritis, renal transplant, congenital heart anomalies, congestive heart failure, cystic fibrosis, human immunodeficiency virus infection, Lyme disease, Kawasaki disease, nephrotic syndrome, and sickle cell anaemia. Children with otitis media were included because previous publications have documented a similar rate of occult bacteraemia regardless of the presence of otitis media.

Laboratory tests were performed as part of the ED visit</td><td>(0.88±0.01) and ANC (0.89±0.01) were significantly better than those for ABC (0.74±0.03) or temperature (0.62±0.03). There was no difference between the ROC curves for WBC and ANC (P = 0.22), but both exhibited greater accuracy than the ROC curves for ABC or temperature (P<.01).

Summary table of the rates of Bacteraemia at Different White Blood Cell Count (WBC) and Temperature Cut-offs
<table>
<tr><td colspan="7">Temperature cut-off, °C. *</td></tr>
<tr><td>WBC cut-off x 10^9/L</td><td>39.0–39.4</td><td>39.5–39.9</td><td>40.0–40.4</td><td>40.5–40.9</td><td>≥41.0</td><td>Row totals</td></tr>
<tr><td>0–4.99</td><td>0/165(0.0)</td><td>0/190(0.0)</td><td>0/111(0.0)</td><td>0/57(0.0)</td><td>0/20(0.0)</td><td>0/543(0.0)</td></tr>
<tr><td>5–9.99</td><td>0/917 (0.0)</td><td>2/1034(0.2)</td><td>1/787(0.1)</td><td>0/431(0.0)</td><td>0/125(0.0)</td><td>3/3294(0.1)</td></tr>
<tr><td>10–14.99</td><td>1/788 (0.1)</td><td>4/830(0.5)</td><td>2/667 (0.3)</td><td>6/384(1.6)</td><td>2/113(1.8)</td><td>15/2785(0.5)</td></tr>
<tr><td>15–19.99</td><td>7/352(2.0)</td><td>9/400(2.2)</td><td>18/339(5.3)</td><td>10/220(4.5)</td><td>4/74(5.4)</td><td>48/1385(3.5)</td></tr>
<tr><td>20–24.99</td><td>6/111(5.4)</td><td>6/146(4.1)</td><td>11/136(8.1)</td><td>9/77(11.7)</td><td>2/33(6.1)</td><td>34/503(6.8)</td></tr>
<tr><td>25–29.99</td><td>5/36 (13.9)</td><td>1/47(2.1)</td><td>3/40(7.5)</td><td>2/30(6.7)</td><td>1/14(7.1)</td><td>12/167(7.2)</td></tr>
<tr><td>30–50</td><td>3/20 (15.0)</td><td>08/22(36.4)</td><td>0/16(0.0)</td><td>2/16(12.5)</td><td>2/8(25.0)</td><td>15/82(18.3)</td></tr>
<tr><td>Total</td><td>22/2389(0.9)</td><td>30/2669(1.1)</td><td>35/2096(1.7)</td><td>29/1215(2.4)</td><td>11/387(2.8)</td><td>127/8756(1.5)</td></tr>
<tr><td colspan="7">* Each cell reports the number f patients with +ve blood culture in the number, the total in the denominator, and the percentage in the parentheses. The number in this table is slightly different in the text as this table represents only those who both WBC and blood culture were obtained.</td></tr>
</table>

Sensitivities and Specificities at Different Cut-off Values for the White Blood Cell Count (WBC)*
<table>
<tr><td>WBC cut-off x 10^9/L</td><td>Sensitivity %</td><td>Specificity %</td><td>PPV %</td><td>Child above predictive value %</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>in accordance with the standard protocol in the department for patients meeting risk criteria for occult bacteraemia. White blood cell counts were performed. True-positive cultures were defined as group A streptococci, group B streptococci, Haemophilus influenzae type b, Neisseria meningitidis, Salmonellae species, and Streptococcus pneumoniae.</td><td>
<table>
<tr><td>≥5</td><td>1.00 (0.96–1.00)</td><td>0.06(0.06–0.07)</td><td>1.6(1.3–1.8)</td><td>1.6 (1.3–1.8)</td></tr>
<tr><td>≥10</td><td>0.98 (0.93–0.99)</td><td>0.44(0.43–0.45)</td><td>2.5(2.1–3.0)</td><td>2.5(2.1–3.0)</td></tr>
<tr><td>≥15</td><td>0.86 (0.78–0.91)</td><td>0.77(0.76–0.77)</td><td>5.1(4.2–6.1)</td><td>5.1(4.2–6.1)</td></tr>
<tr><td>≥16</td><td>0.77 (0.69–0.84)</td><td>0.81(0.80–0.82)</td><td>5.6(4.6–6.9)</td><td>5.6(4.6–6.9)</td></tr>
<tr><td>≥17</td><td>0.72 (0.64–0.80)</td><td>0.84(0.84–0.85)</td><td>6.4(5.2–7.9)</td><td>6.4(5.2–7.9)</td></tr>
<tr><td>≥18</td><td>0.64(0.55–0.72)</td><td>0.87(0.86–0.88)</td><td>6.8(5.5–8.4)</td><td>6.8(5.5–8.4)</td></tr>
<tr><td>≥19</td><td>0.56 (0.47–0.65)</td><td>0.90(0.89–0.90)</td><td>7.5(6.0–9.4)</td><td>7.5(6.0–9.4)</td></tr>
<tr><td>≥20</td><td>0.48(0.39–0.57)</td><td>0.92(0.91–0.93)</td><td>8.1(6.3–10.4)</td><td>8.1(6.3–10.4)</td></tr>
<tr><td colspan="5">*(): 95% CIs
NPV not specified.</td></tr>
</table>
A total of 586 patients visited the ED in the 12 weeks represented by the first week of each month of 1996. Of these patients, 8 (1.4%) were found to have an incorrectly coded discharge diagnosis recorded in the computer database. Eighty-nine patients (15.2%) were recently or currently being treated with antibiotics and 1 patient had been immunized within the previous 48 hours.
</td></tr>
<tr><td>Kuppermann[284]

Study type :
prospective cohort study
EL:2+</td><td>Country:
US
Condition:
Occult pneumococcal bacteraemia (OPB)
Aim:
The purpose of this study was to identify predictors of OPB among a large cohort of young, febrile children treated as outpatients using multivariable statistical methods.
Setting, inclusion/exclusion:
They evaluated 6,579</td><td>In total 6579 patients were included (6680 were recruited with 110 exclusion, reasons of exclusion were adequately described.)

Generation of derivation and validation sets
They randomly selected two thirds of this population (n = 4384 (66.6%), 109 (2.5%) had bacteraemia) for the derivation of the model and one third for validation. In the derivation set, they analyzed the univariate relationships of six variables with OPB: age, temperature, clinical score, WBC count, absolute neutrophil count (ANC), and absolute band count (ABC). All six variables were then entered into a logistic regression equation and those retaining statistical significance were considered to have an independent association with OPB.

Table :Comparison of patients in the deviation and validation sets.
<table>
<tr><td>Characteristic*</td><td>Deviation</td><td>Validation</td><td>P value</td></tr>
<tr><td>N (%) of subjects</td><td>4384 (67%)</td><td>2195 (33%)</td><td>--</td></tr>
<tr><td>N (%) with OPB</td><td>109 (2.5)</td><td>55 (2.5%)</td><td>0.96</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr>
<td></td>
<td>outpatients 3 to 36 months of age with temperatures of 39 degrees C or higher who previously had been enrolled in a study of young febrile patients at risk of OPB in the emergency departments of 10 hospitals in the United States between 1987 and 1991. Outpatients 3 to 36 months of age with temperatures of 39 degrees C or higher who previously had been enrolled in a study of young febrile patients at risk of OPB in the emergency departments. Exclusion criteria were: patients with a toxic clinical appearance requiring hospitalisation, the presence of a specific viral infection (e.g. croup, varicella) or focal bacterial infection other than otitis media (e.g. Cellulites, UTI, meningitis), a known immunodeficiency or chronic illness that would affect the approach to a febrile illness, or immunisation or antibiotic therapy within the preceding 48 hrs. Blood samples were obtained from each patient; a CBC was strongly encouraged but not required, and was performed for 5695 (89%) patients.</td>
<td>
<table>
<tr><td>Age (months)</td><td>14.2 ± 8.0</td><td>14.3 ± 8.2</td><td>0.73</td></tr>
<tr><td>Median YOS (range)</td><td>6 (6–24)</td><td>6(6–18)</td><td>0.39</td></tr>
<tr><td>Temperature (°C)</td><td>39.8 ± 0.6</td><td>39.8 ± 6.6</td><td>0.30</td></tr>
<tr><td>WBC (x10^3/mm^3)**</td><td>13.1 ± 6.7</td><td>13.1 ± 6.6</td><td>0.91</td></tr>
<tr><td>ANC (x10^3/mm^3)**</td><td>7.4 ± 5.2</td><td>7.5 ± 5.1</td><td>0.75</td></tr>
<tr><td>ABC(x10^3/mm^3)**</td><td>0.99 ± 1.3</td><td>0.95 ± 1.1</td><td>0.26</td></tr>
<tr><td colspan="4">*: values are mean ± SD unless noted otherwise.
**: WBC obtained on 89% patients; ANC and ABC obtained on 83% patients.</td></tr>
</table>

164 patients (2.5%) had OPB. Patients with OPB were younger, more frequently ill-appearing, and had higher temperatures, WBC, ANC, and ABC than patients without bacteraemia. Only three variables, however, retained statistically significant associations with OPB in the multivariate analysis.
Table :Univariate analysis of the deviation set
<table>
<tr><td>Characteristic *</td><td>OPB(n = 109)</td><td>Non-OPB(n = 4275)</td><td>Difference between means or Odds Ratio for %$^+$ (95% CI)</td><td>P value</td></tr>
<tr><td>Age (months)</td><td>14.17 ± 6.94</td><td>1423 ± 8.05</td><td>−0.06(−1.40 to 1.28)</td><td>0.93</td></tr>
<tr><td>Age < 2yr (n,%)</td><td>99 (91%)</td><td>3670 (86%)</td><td>1.63 (0.86–3.11)</td><td>0.14</td></tr>
<tr><td>Median YOS (range)</td><td>6(6–14)</td><td>6(6–24)</td><td>--</td><td>< 0.001</td></tr>
<tr><td>YOS> 6 (n,%)</td><td>34 (31%)</td><td>751 (18)</td><td>2.12(1.41–3.20)</td><td>< 0.001</td></tr>
<tr><td>Temperature (°C)</td><td>40.04 ± 0.58</td><td>39.78 ± 0.55</td><td>0.26(0.16–0.37)</td><td>< 0.001</td></tr>
<tr><td>WBC (x10^3/mm^3)</td><td>21.49 ± 8.21</td><td>12.90 ± 6.54</td><td>8.59(6.89–10.3)</td><td>< 0.001</td></tr>
<tr><td>ANC (x10^3/mm^3)</td><td>14.70 ± 7.06</td><td>7.25 ± 4.97</td><td>7.45(5.99–8.93)</td><td>< 0.001</td></tr>
<tr><td>ABC(x10^3/mm^3)</td><td>2.133 ± 2.32</td><td>0.96 ± 1.26</td><td>1.17(0.68–1.64)</td><td>< 0.001</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td></td><td>
*: values are mean ± SD unless noted otherwise.

+: OR: odds ratio. OR denoting the increased odds of OPB are given for categorical variables < 2 years vs. 2–3 yrs, YOS> 6 vs. YOS = 6; differences in mean values between patients with and without OPB are given for continuous variables.

The multivariate analysis: ANC (Adjusted odds ratio [OR] 1.15 for each 1,000 cells/mm3 increase, 95% confidence interval [CI] 1.06, 1.25), temperature (adjusted OR 1.77 for each 1 degree C increase, 95% CI 1.21, 2.58), and age younger than 2 years (adjusted OR 2.43 versus patients 2 to 3 years old, 95% CI interval 1.11, 5.34). In the derivation set, 8.1% of patients with ANCs greater than or equal to 10,000 cell/mm3 had OPB (95% CI 6.3, 10.1%) versus .8% of patients with ANCs less than 10,000 cells/mm3 (95% CI .5, 1.2%). When tested on the validation set, the model performed similarly.

Table :Logistic regression analysis of the derivation set
<table>
<tr><td>Predictor</td><td>OR*</td><td>95% CI</td><td>P value</td></tr>
<tr><td>ANC</td><td>1.15</td><td>1.06–1.25</td><td>0.001</td></tr>
<tr><td>Temperature (°C)</td><td>1.77</td><td>1.21–2.58</td><td>0.003</td></tr>
<tr><td>Age < 2yr (n,%)</td><td>2.43</td><td>1.11–5.34</td><td>0.03</td></tr>
<tr><td>YOS> 6 (n,%)</td><td>1.23</td><td>0.74–2.04</td><td>0.42</td></tr>
<tr><td>WBC (x10^3/mm^3)</td><td>1.01</td><td>0.95–1.08</td><td>0.77</td></tr>
<tr><td>ABC(x10^3/mm^3)</td><td>1.02</td><td>0.91–1.14</td><td>0.71</td></tr>
<tr><td colspan="4">*: the Ors described odds of PPB for the following increments in the predictive values: (1) and increase in ANC, WBC and ABC of 1000 cell/mm^3 , (2) a one degree C increase in temperature, (3) patients < 2yr vs. pt 2–3 years and (4) patients with YOS > 6 vs. YOS = 6.</td></tr>
</table>
</td></tr>
<tr><td>Mahabee-Gittens[139]</td><td><u>Country:</u></td><td>Children were recruited and enrolled 2 evenings weekly though the 18-months period.

During the study recruitment hours, 900 were excluded with clearly documented reasons. Of the remaining 636 patients who met</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td>Study type :
prospective cohort study

EL: 2+</td><td>USA
Condition:
Pneumonia
Aim:
To identify a set of clinical variables that may help to clinically differentiate children with and without radiographic evidence of pneumonia.
Setting, inclusion/exclusion
ER of the Cincinnati Children’s Hospital Medical Centre, Ohio between June 2000 and January 2002.
A subject could be enrolled more than once if the visits to the ER is more than 6 months apart. Children (2–59 months) with one or more of the following symptoms: laboured, rapid, or noisy breathing; chest or abdominal pain; or fever. Patients were excluded if they were currently taking antibiotics; presented to the ER for treatment of smoke inhalation, foreign body aspiration, or chest trauma; or had known diagnostic trauma; or had known diagnoses of asthma, bronchiolitis, cystic fibrosis, sickle cell disease or chronic cardiopulmonary disease.
Evaluations include presence or</td><td>inclusion criteria, the parents or legal guardians of 99 could not be reached or refused to consent. The 126 patients who did not participate and 510 who were enrolled in this study had baseline comparability. That left the total number of the study as 510.
In this prospective cohort study 100% were evaluated with chest radiography and 44 (8.6%) had pneumonia on chest radiography.

Table :Characteristics of subjects with and without radiographic evidence of pneumonia
<table>
<tr><td>Characteristics</td><td>Pneumonia(n = 44)</td><td>No pneumonia (n = 466)</td><td>P</td></tr>
<tr><td></td><td colspan="3">Mean ± SD</td></tr>
<tr><td>Age (m)</td><td>20.9 ± 17.2</td><td>14.8 ± 13.4</td><td>0.005</td></tr>
<tr><td>Respiratory rate (per minute)</td><td>49.8 ± 14.2</td><td>42.7 ± 13.3</td><td>0.01</td></tr>
<tr><td>Temperature (°F)</td><td>100.8 ± 2.2</td><td>100.2 ± 2.1</td><td>0.1</td></tr>
<tr><td>Heart rate (per minute)</td><td>145.5 ± 25.9</td><td>148.8 ± 25.6</td><td>0.4</td></tr>
<tr><td>Oxygen saturation (%)</td><td>95.5 ± 2.0</td><td>97.8 ± 2.2</td><td>0.001</td></tr>
<tr><td>Characteristics</td><td>Pneumonia(n = 44)</td><td>No pneumonia (n = 466)</td><td>P</td></tr>
<tr><td></td><td colspan="3">No of subjects (column%)</td></tr>
<tr><td>Autumn or winter visit</td><td>37 (84.1%)</td><td>330 (70.8%)</td><td>0.06</td></tr>
<tr><td>Breast-fed</td><td>3(6.8%)</td><td>34 (7.3%)</td><td>0.9</td></tr>
<tr><td>Daycare or pre-school</td><td>18 (40.9%)</td><td>160 (34.4%)</td><td>0.4</td></tr>
<tr><td>Smokers in the home</td><td>18 (40.9%)</td><td>232 (49.9%)</td><td>0.3</td></tr>
<tr><td>Siblings in the home</td><td>28 (63.6%)</td><td>306 (65.8%)</td><td>0.7</td></tr>
<tr><td>Illness duration > 48 hr</td><td>30 (68.2%)</td><td>307 (66%)</td><td>0.7</td></tr>
<tr><td>Nasal flaring</td><td>10 (22.7%)</td><td>36 (7.7%)</td><td>0.001</td></tr>
<tr><td>Grunting</td><td>1 (2.4%)</td><td>19 (4.4%)</td><td>0.5</td></tr>
<tr><td>Retraction</td><td>14 (31.8%)</td><td>134 (28.8%)</td><td>0.7</td></tr>
<tr><td>Crackles</td><td>9 (20.5%)</td><td>63 (13.5%)</td><td>0.2</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>absence of irritability, grunting, nasal flaring, accessory muscle use, decreased breath sounds, crackles and wheezing.</td><td>
<table>
<tr><td>Decreased breath sounds</td><td>5 (11.4%)</td><td>24 (5.2%)</td><td>0.09</td></tr>
<tr><td>wheezing</td><td>9 (20.5%)</td><td>76 (16.3%)</td><td>0.5</td></tr>
</table>
With use of multivariate analysis, the adjusted odds ratio (AOR) and 95% confidence intervals (CI) of the clinical findings significantly associated with focal infiltrates were age older than 12 months (AOR 1.4, CI 1.1–1.9), RR 50 or greater (3.5, CI 1.6–7.5), oxygen saturation 96% or less (AOR 4.6, CI 2.3–9.2), and nasal flaring (AOR 2.2 CI 1.2–4.0) in patients 12 months of age or younger. The combination of age older than 12 months, RR 50 or greater, oxygen saturation 96% or less, and in children under age 12 months, nasal flaring, can be used in determining which young children with lower respiratory tract infection symptoms have radiographic pneumonia.
Table : sensitivity, specify and likelihood ratio (LR) of different cut-offs of Respiratory Rate and oxygen saturation.
<table>
<tr><td>Variable</td><td>Sensitivity % (95% CI)</td><td>Specificity (95% CI)</td><td>(95% CI)</td></tr>
<tr><td>Age > 12 months</td><td>0.66(0.51–0.78)</td><td>0.57(0.53–0.62)</td><td>1.5(1.2–1.9)</td></tr>
<tr><td>Respiratory rate (per minute)</td><td></td><td></td><td></td></tr>
<tr><td>≥40</td><td>0.77(0.63–0.87)</td><td>0.43(0.39–0.48)</td><td>1.4(1.1–1.6)</td></tr>
<tr><td>≥ 50</td><td>0.50(0.36–0.64)</td><td>0.71(0.67–0.75)</td><td>1.7 (1.3–2.4)</td></tr>
<tr><td>≥ 60</td><td>0.32(0.20–0.18)</td><td>()</td><td>()</td></tr>
<tr><td>≥ 70</td><td>0.07 (0.02–0.18)</td><td>0.97 (0.95–0.98)</td><td>2.1 (0.6–7.1)</td></tr>
<tr><td>Oxygen saturation (%)</td><td></td><td></td><td></td></tr>
<tr><td>≤96</td><td>0.63 (0.48–0.76)</td><td>0.77 (0.74–0.81)</td><td>2.8 (2.1–3.7)</td></tr>
<tr><td>≤ 95</td><td>0.42 (0.28–0.57)</td><td>0.88 (0.85–0.91)</td><td>3.5 (2.3–5.4)</td></tr>
<tr><td>≤ 94</td><td>0.26 (0.15–0.24)</td><td>0.96 (0.94–0.98)</td><td>3.0 (1.2–7.5)</td></tr>
<tr><td>≤ 93</td><td>0.12(0.05–0.24)</td><td>0.96 (0.94–0.98)</td><td>3.0 (1.2–7.5)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Nasal flaring (< = 12 months)</td><td>0.33 (0.15–0.58)</td><td>0.94 (0.90–0.96)</td><td>5.2 (2.2–12.2)</td></tr>
<tr><td colspan="4">Likelihood ratio: sensitivity/(1- specificity).</td></tr>
</table>

Table :Proportion of subjects with pre-test probabilities of pneumonia in the following ranges : < 25%, 25–50, 51–75% or > 75%.
<table>
<tr><td>Physician pre-test probability of pneumonia</td><td>Pneumonia (n = 44)</td><td>No pneumonia (n = 466)</td></tr>
<tr><td>< 25%</td><td>25 (56.8%)</td><td>303 (65%)</td></tr>
<tr><td>25–50 %</td><td>13 (29.5%)</td><td>107 (23%)</td></tr>
<tr><td>51–75</td><td>5 (11.4%)</td><td>51 (11%)</td></tr>
<tr><td>> 75 %</td><td>1 (2.3%)</td><td>5 (1%)</td></tr>
</table>
There were no statistic significances in the pre-test probabilities assigned to patients with and without radiographic evidence of pneumonia. If the physician’s cut off point for ordering chest radiography had been a pre-test probability of < 25%, they would have missed out 25 (56.8%) of the 44 subjects with radiographic pneumonia and ordered unnecessary chest radiographs in 163 (35%) of 466 children without radiographic pneumonia.

Table : sensitivity, specificity, and likelihood ratios of the model at different cut points (PPVs and NPVs not reported)
<table>
<tr><td>Age > 12m</td><td>RR ≥50/minute</td><td>O2 Sat ≤ 96%</td><td>Nasal flaring</td><td>Sensitivity % (95% CI)</td><td>Specificity % (95% CI)</td><td>Likelihood ration % (95% CI)</td></tr>
<tr><td>v</td><td>v</td><td>v</td><td></td><td>0.18 (0.10–0.32)</td><td>0.97 (0.95–0.98)</td><td>6.1 (2.7–13.6)</td></tr>
<tr><td>v</td><td></td><td>v</td><td></td><td>0.41 (0.28–0.56)</td><td>0.91 (0.88–0.93)</td><td>4.5 (2.9–7.2)</td></tr>
<tr><td></td><td>v</td><td>v</td><td></td><td>0.34 (0.22–0.49)</td><td>0.92 (0.89–0.94)</td><td>4.3 (2.6–7.2)</td></tr>
<tr><td>v</td><td>v</td><td></td><td></td><td>0.25 (0.15–0.40)</td><td>0.93 (0.91–0.95)</td><td>3.6 (2.0–6.7)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td></td><td>v</td><td></td><td>0.63 (0.48–0.76)</td><td>0.77 (0.74–0.81)</td><td>2.8 (2.1–3.7)</td></tr>
<tr><td></td><td>v</td><td></td><td></td><td>0.50 (0.36–0.64)</td><td>0.71 (0.67–0.75)</td><td>1.7 (1.3–2.4)</td></tr>
<tr><td></td><td>v</td><td>v</td><td>v</td><td>0.20 (0.07–0.45)</td><td>0.98 (0.95–0.99)</td><td>11.0 (2.4–49.8)</td></tr>
<tr><td colspan="7">Check mark (v) indicates that the presence of the given variables included in the prediction.</td></tr>
</table>
</td></tr>
<tr><td>Taylor[140]

Study type :
prospective cohort study

EL:2+</td><td>Country:
USA
Condition:
Pneumonia
Aim:
To determine values for defining tachypnoea in febrile children younger than 2 years that best identify those at risk for pneumonia.
Setting, inclusion/exclusion:
From January 1992 to December 1992.
Children younger than 2 years presenting to the emergency department of a children’s hospital and medical centre, Seattle with a temperature of 38 degree C or higher. Children were excluded if they presented with acute wheezing and/or stridor or if they had a history of</td><td>
Data were analyzed for 572 children; pneumonia was present in 42 (7%). Pneumonia was present on 41 (33%) radiographs out of 123 initial order, and 85 (65%) showed no pneumonia radiographs of two children were categorised as indeterminate by both radiologists and their data were excluded.

Though the temperature distribution was not different in the two groups, patients with high fever (> = 40 °C) were more likely to have pneumonia (P value not provided). Among the 62 children with a temperature > = 40 °C, 16% had pneumonia. Other details about fever were not reported.

Table :The clinical characteristics of two groups of children
<table>
<tr><td>Variable</td><td>No pneumonia (n = 530)</td><td>Pneumonia (n = 42)</td><td>P</td></tr>
<tr><td>Age (months)</td><td>11.0 (6.0)</td><td>12.5 (6.3)</td><td>0.131</td></tr>
<tr><td>Temp. (°C)</td><td>39.0 (0.70)</td><td>39.1 (0.84)</td><td>0.108</td></tr>
<tr><td>RR (/minute)</td><td>42.1 (12.6)</td><td>52.7 (13.9)</td><td>< 0.01</td></tr>
<tr><td colspan="4">Values were presented as mean (SD)</td></tr>
</table>

There was significant decrease in RR between children aged 2–5 months and aged 6–11 months (P = 0.004), and between those aged 6–11 and those aged 12–17 months (P< 0.001).

Table :The sensitivity, specificity, PPV and NPV of tachypnoea as a sign of pneumonia.
<table>
<tr><td>Age group</td><td>Sensitivity % (95% CI)</td><td>Specificity % (95% CI)</td><td>PPV % (95% CI)</td><td>NPV % (95% CI)</td><td>Risk Ratio</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>chronic pulmonary disease.

The respiratory rate (RR) was obtained by physician or nurse practitioner by standardised method for 1 year. Study patients were classified as having pneumonia (n = 42) or no pneumonia (n = 530) based on clinical evaluation and chest radiograph findings. If both of the two radiologists interpreted a radiograph as indeterminate, that child was excluded,

Receiver operating characteristic curves were constructed to select the values for respiratory rate that maximized sensitivity and specificity of tachypnoea as a sign of pneumonia.</td><td>
<table>
<tr><td>0–5 months (n = 121)</td><td>83.3 (76.7–89.9)</td><td>79.1 (71.9–86.3)</td><td>17.2 (10.5–23.9)</td><td>98.9 (96.0–100.0)</td><td>15.6(2.62-∞)</td></tr>
<tr><td>6–11 months (n = 213)</td><td>66.7(60.3–73.1)</td><td>79.1 (67.8–79.0)</td><td>16.0 (11.1–20.9)</td><td>97.5 (95.4–99.6)</td><td>6.4(2.41–52.3)</td></tr>
<tr><td>1–2 years (n = 238)</td><td>70.8 (65.0–76.6)</td><td>73.4 (67.8–79.0)</td><td>23.0 (17.7–28.3)</td><td>95.7 (94.4–97.0)</td><td>5.35(3.16–9.43)</td></tr>
<tr><td>All (n = 572)</td><td>73.8 (70.2–77.4)</td><td>76.8 (77.3–80.3)</td><td>20.1 (16.8–23.4)</td><td>97.4 (96.1–98.7)</td><td>7.73(4.31–18.0)</td></tr>
</table>

The diagnostic utility of tachypnoea was maximal when cut-off values for respiratory rates of 59/minute in infants younger than 6 months, 52/minute in those aged 6 through 11 months, and 42/minute in those aged 1 to 2 years were selected. Based on these definitions, 31/42 (73.8%) children with pneumonia were tachypnoeic vs. 123/530 (23.2%) without pneumonia (P< 0.001). Tachypnoea as a sign of pneumonia had a sensitivity of 73.8%, specificity of 76.8%, positive predictive value of 20.1%, negative predictive value of 97.4% and risk ration of 7.73.

In the regression model, the presence of pneumonia was positively associated with respiratory rate (P< 0.001); temperature was also positively related with respiratory rate (P = 0.002); the regression coefficient between reparatory rate and temperature was 2.5.</td></tr>
<tr><td>Lucero[141]

<u>Study type</u> :

prospective cohort study

EL: 2+</td><td><u>Country:</u>

Philippines

<u>Condition:</u>

Pneumonia

<u>Aim:</u>

Test the validity of RR> 50/minute as an indicator of pneumonia.

<u>Setting inclusion/exclusion:</u>

This is part of a larger study on the diagnoses and epidemiology of acute respiratory tract infection in children < 5 in</td><td>The prevalence of pneumonia if the first group was 69% and 29% in the second group. Radiographically diagnosed pneumonia was used as the gold standard by which to test the validity of tachypnoea (RR> 50/minute).

Table :Validation of RR> 50/minute of pneumonia in two populations of children in which the prevalence of pneumonia differs.
<table>
<tr><th>RR</th><th>Presence of RR</th><th>No of children with/without pneumonia</th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>PPV (%)</th><th>NPV (%)</th><th>Risk ratio</th></tr>
<tr><td colspan="8">Group 1</td></tr>
<tr><td>> 50/minute</td><td>Yes</td><td>74/10</td><td>54</td><td>84</td><td>88</td><td>44</td><td>1.57</td></tr>
<tr><td></td><td>No</td><td>64/51</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>> 40/minute</td><td>Yes</td><td>101/26</td><td>73</td><td>57</td><td>80</td><td>49</td><td>1.57</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>Manila.

The first group was studied from July 1984 to June 1985, while the second group was studied from May 1988 to January 1989.

Two groups of children were studied: the first group presented at outpatient clinic on the Research Institute of Tropical Medicine for cough < 3 weeks; the second group presented at the outpatient department of the Makati Medical Centre for cough < 1 week.

Other details were not reported.

In both groups, RR was measured when the child was quiet or a sleep.</td><td>
<table>
<tr><td></td><td>No</td><td>37/35</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="8">Group 2</td></tr>
<tr><td>> 50/minute</td><td>Yes</td><td>11/24</td><td>19</td><td>83</td><td>31</td><td>71</td><td>1.01</td></tr>
<tr><td></td><td>No</td><td>47/115</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>> 40/minute</td><td>Yes</td><td>26/45</td><td>45</td><td>68</td><td>37</td><td>75</td><td>1.48</td></tr>
<tr><td></td><td>No</td><td>32/96</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>> 50/minute + SC*</td><td>Yes</td><td>19/29</td><td>33</td><td>79</td><td>40</td><td>74</td><td>1.54</td></tr>
<tr><td></td><td>No</td><td>39/112</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>> 40/minute + SC</td><td>Yes</td><td>28/46</td><td>48</td><td>68</td><td>38</td><td>76</td><td>1.58</td></tr>
<tr><td></td><td>No</td><td>30/95</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="8">*SC: symptoms of complex including chest retraction and/or cyanosis and/or failure to eat normally, details not reported.</td></tr>
</table>
</td></tr>
<tr><td>Gupta[142]

Study type :

prospective cohort study

EL: 2+</td><td>Country

India

Condition :

Pneumonia

Aim:

To study simple signs for the diagnosis of pneumonia.

Setting, inclusion/exclusion:

A hospital based study. All children < 5 years presenting to the paediatric outpatients or ED were screened for lower</td><td>In total, 222 children were included. After clinical assessment, there were 91 (41%) had no pneumonia, 36 (16%) with pneumonia, 73 (33%) with severe pneumonia and 22 (10%) with very severe pneumonia. There were 125 (56%) radiologically confirmed pneumonia.

Table :Sensitivity, specificity, PPV and NPV for various clinical feature.
<table>
<tr><td>Feature*</td><td>Sensitivity %</td><td>Specificity %</td><td>PPV %</td><td>NPV %</td><td>RR</td></tr>
<tr><td>Cough</td><td>10</td><td>0</td><td>24</td><td>0</td><td>--</td></tr>
<tr><td>Difficult breathing</td><td>57</td><td>98</td><td>90</td><td>88</td><td>7.5</td></tr>
<tr><td>History of turning blue</td><td>2</td><td>100</td><td>100</td><td>76</td><td>3.85</td></tr>
<tr><td>Feeding difficulty</td><td>15</td><td>100</td><td>100</td><td>79</td><td>4.76</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>respiratory infections. All children suspected to have lower respiratory infections were subjected to have chest radiography. Every 5th child found to have acute upper respiratory infections was subjected to have chest radiography. Exclusion not reported.</td><td>
<table>
<tr><td>Altered sensorium</td><td>2</td><td>100</td><td>100</td><td>76</td><td>4.17</td></tr>
<tr><td>Fever</td><td>95</td><td>36</td><td>32</td><td>96</td><td>8.0</td></tr>
<tr><td>Vomiting</td><td>16</td><td>83</td><td>22</td><td>76</td><td>0.92</td></tr>
<tr><td>Loose stools</td><td>14</td><td>78</td><td>17</td><td>74</td><td>0.65</td></tr>
<tr><td>Fast breathing</td><td>83</td><td>98</td><td>93</td><td>95</td><td>18.6</td></tr>
<tr><td>Chest indrawing</td><td>62</td><td>98</td><td>92</td><td>89</td><td>8.36</td></tr>
<tr><td>Cyanosis</td><td>3</td><td>100</td><td>100</td><td>77</td><td>4.38</td></tr>
<tr><td>Pyrexia</td><td>72</td><td>64</td><td>39</td><td>88</td><td>3.25</td></tr>
<tr><td>Crepitations</td><td>81</td><td>99</td><td>97</td><td>94</td><td>16.2</td></tr>
<tr><td>Rhonchi</td><td>9</td><td>99</td><td>92</td><td>77</td><td>4.0</td></tr>
<tr><td>Hepatomegaly</td><td>38</td><td>97</td><td>82</td><td>83</td><td>3.03</td></tr>
<tr><td colspan="6">All the features were not defined/described in detail in the text.</td></tr>
</table>

The authors explored different definitions of fast breathing and t hey found a cut-off point at 50 or 60/minute have almost equal sensitivity and specificity. Respiratory Rate> 50/minute is the best indicator in children aged 2–11 months. Respiratory Rate = 40/minute is best for children 12–35 months and cut-off at 30/minute is best for children 36–60 months.
</td></tr>
<tr><td>Shamo'on[143]

Study type :
prospective cohort study

EL: 2+</td><td>Country:
Jordan
Condition:
Pneumonia
Aim :
To emphasize the importance of using simple clinical signs such as respiratory rate and chest</td><td>The 147 patients in the study were divided into 2 groups according to the chest X-ray findings: those having lobar pneumonia or bronchopneumonia in 1 or more lobes, and those having normal or hyperinflated chest X-rays. The clinical signs and symptoms of the 2 groups were analysed and compared with the radiological evidence of pneumonia (gold standard).This study included 147 children admitted with clinical pneumonia, 72 (49%) male and 75 (51%) female. The ages of the children were: 1–12 months 92 (63%), 13–36 months 47 (32%) and 37–72 months 8 (5%). Mean duration of admission was 5 days for the first and second age groups and 2 days for the third age group. From the chest X-ray findings, 40 children (27%) had lobar pneumonia in 1 or 2 lobes and 50 children (34%) had broncho-pneumonia, a total of 90 children (61%) with pneumonia diagnosed on a radiological basis. Fifty-seven children (39%) had normal or hyperinflated chest X-rays. A family history of bronchial asthma or allergy was discovered in 15 children (10%).</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>wall indrawing in detecting ALRI, especially pneumonia, in children.

<u>Setting, inclusion/exclusion:</u>

A prospective clinical observation study at Queen Alia Military Hospital, Amman, Jordan over a 6-month period (August 2002–January 2003) for all children below 6 years of age admitted with clinical pneumonia (most cases admitted were below this age). All patients were admitted via the outpatient clinic at Marqa, which is about 20 km from the hospital. This clinic sees patients from areas surrounding Amman (suburban areas) but does not always have radiology facilities available. The paediatrician admitted all cases on a clinical basis according to World Health Organization criteria: cough with tachypnoea (respiratory rate > 50/minute in infants or > 40/minute in older children), indrawing or wheezing. The respiratory rate was counted for a full minute after lowering the temperature (using cold compresses or paracetamol) to < 38 °C rectally or 37.5 °C axillary and before the routine extraction of blood. All children admitted were examined by a specialist in</td><td>Table : Signs and symptoms to predict pneumonia
<table><tr><td></td><td colspan="2">Chest x ray</td><td>Sensitivity %</td><td>Specificity %</td></tr><tr><td>Clinical features</td><td>Pneumonia detected (n = 90)

No. +ve for signs & symptoms</td><td>Normal hyperinflated (n = 57)

No. +ve for signs & symptoms89</td><td></td><td></td></tr><tr><td>Tachypnoea</td><td>89</td><td>7</td><td>99</td><td>88</td></tr><tr><td>Cough</td><td>88</td><td>17</td><td>98</td><td>70</td></tr><tr><td>Chest indrawing</td><td>79</td><td>13</td><td>88</td><td>77</td></tr><tr><td>Fever</td><td>70</td><td>33</td><td>78</td><td>42</td></tr><tr><td>Poor feeding</td><td>52</td><td>27</td><td>58</td><td>53</td></tr><tr><td>Grunting</td><td>52</td><td>27</td><td>58</td><td>53</td></tr><tr><td>Diminished air entry</td><td>30</td><td>28</td><td>33</td><td>51</td></tr><tr><td>Crepitation</td><td>27</td><td>25</td><td>30</td><td>56</td></tr><tr><td>Wheezes</td><td>20</td><td>29</td><td>22</td><td>49</td></tr></table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>paediatrics and the same ear, nose and throat specialist to exclude severe upper respiratory tract infection and all had chest X-rays which were assessed by the same radiologist. Exclusion criteria from the study were children with immune deficiency, those known to have asthma, history of foreign body aspiration or chemical pneumonitis, children with failure to thrive and malnutrition, and children with severe upper respiratory tract infection. Malnourished children were excluded</td><td></td></tr>
<tr><td>Redd[144]

<u>Study type</u> :
prospective cohort study
EL:2+</td><td><u>Country :</u>
Lesotho
<u>Condition:</u>
Pneumonia
<u>Aim:</u>
The value of clinical findings for the diagnosis of pneumonia.
<u>Setting, inclusion/exclusion:</u>
This study was done in Queen Elizabeth II Hospital, the central referral hospital for Lesotho. About 40 under-five-year-olds were seen in this hospital at each working day.
Children aged 3 months to 5 years with a cough, blocked or</td><td>A total of 950 children with respiratory infection were potentially eligible for the study (277 at high risk and 673 at low risk for pneumonia). All the high-risk children and 128/134 (96%) of low-risk children were enrolled. A total of 382 (94%) of those enrolled) were examined by the GP and 251 (62% of those enrolled) were examined by the paediatrician. Chest radiographs were available for 393 children (97% of those enrolled).
The median age was 11.8 months (range, 3–59 months); high-risk children were significantly younger (rank test, P< 0.001).
Table: prevalence of elevated RR, measured by nurse, GP and paediatrician, and radiographic evidence of pneumonia.
<table>
<tr><td></td><td colspan="3">Measured by nurse</td><td colspan="3">Measured by GP</td><td colspan="3">Measured by paediatrician</td></tr>
<tr><td>Age (months)</td><td>N*</td><td>≥50</td><td>≥40</td><td>N*</td><td>≥50</td><td>≥40</td><td>N*</td><td>≥50</td><td>≥40</td></tr>
<tr><td>Sensitivity[A]</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>3–11</td><td>22/2</td><td>59</td><td>84</td><td>21/2</td><td>65</td><td>81</td><td>14/1</td><td>79</td><td>100</td></tr>
</table>
</td></tr>
</table>

Citation/EL	Methodology	Results

runny nose, ear pain, or breathing difficulty , who were brought to the OPD over a 3-months period were eligible for enrolment. Children were classified as high- and low-risk groups based on the initial assessment. Children with a history of rapid breathing, difficulty in drinking, elevated RR (> 40/minute for > = 12 months; > 50/minute for 3–12 months)., wheezing, nasal flaring, or chest indrawing were defined as at risk of pneumonia. Children without any of those findings were classified as low risk. All high-risk group children and a systematically selected 20% sample of the low-risk children underwent further standard clinical examinations.

The RR was measured for one minute using electronic sounding timers on calm, awake children. The proportion of children who were crying and could not be consoled at the time of exam ranged between 1% to 4% for three examiners (GP, paediatrician and nurse) and the results were included for analysis. The radiographs were reviewed in the US after the end of patient enrolment. Pneumonia was defined as the presence of a pulmonary parenchymal density compatible

12–23	19/4	41	49	18/4	40	42	13/4	21	73
≥24	11/6	24	27	11/6	15	27	6/3	14	24
Specificity[B]									
3–11	132/29	72	44	124/29	60	24	90/21	59	25
12–23	44/32	90	64	42/32	76	48	30/22	85	52
≥24	16/45	97	87	16/41	96	83	10/24	97	88

*:no of children at high risk/no of children at low risk.

A: sensitivity to identify children with radiographic evidence of pneumonia (each number of high-risk child and weight each observation for low-risk child by 5).

B: specificity to identify children without radiographic evidence of pneumonia (each number of high-risk child and weight each observation for low-risk child by 5).

Table : clinical findings, reported by GP, nurse and paediatrician for identification of the study children with radiographic evidence of pneumonia.

	Nurse		GP		Paediatrician	
Age (months)	Fast breathing*	Nasal flaring	Nasal flaring	Crepitations	Nasal flaring	Crepitations
Sensitivity[A]						
3–11	69	19	42	19	32	32
12–23	49	24	26	13	27	27
≥24	24	8	17	32	14	38
Specificity[B]						
3–11	51	93	93	93	95	96
12–23	71	97	95	89	94	87
≥24	92	99	90	92	93	87

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>with pneumonia won chest radiography as interpreted by the paediatric radiologist in the US.</td><td>*: history reported by mother.

A: sensitivity to identify children with radiographic evidence of pneumonia (each number of high-risk child and weight each observation for low-risk child by 5).

B: specificity to identify children without radiographic evidence of pneumonia (each number of high-risk child and weight each observation for low-risk child by 5).</td></tr>
<tr><td>March[286]

Study type :

prospective cohort study (higher risk to confounding)

EL:2-

(inadequate description of sampling frame and may subject to confounding)</td><td>Country:

Brazil.

Condition:

Community acquired Pneumonia

Aim:

Evaluation of the clinical signs and symptoms predicting bacterial and viral pneumonia, in accordance with the Brazilian National Control Program for Acute Respiratory (ARI).

Setting and inclusion/exclusion:

The study was performed at the Pediatric Emergency Service of the Instituto de Puericultura e Pediatria Martagão Gesteira (IPPMG) of the Universidade Federal do Rio de Janeiro (UFRJ), from January 1 to December 31, 1996. This is a study with prospective data collection.</td><td>The cases of pneumonia (n = 76), based on the radiological aspect (gold-standard), were subdivided according to the possible aetiology. Among these patients, 47 presented condensation or pleural effusion, considered cases of bacterial pneumonia, and 29 had infiltrate, considered cases of viral pneumonia.

The 76 patients with pneumonia, based on the radiological pattern, were divided into two groups: a) Group with bacterial pneumonia: 47 children b) Group with viral pneumonia: 29 children.

Table :Findings in infants 0–6 months with bacterial pneumonia
<table>
<tr><th>Feature</th><th>N/T</th><th>%</th><th>Sensitivity%</th><th>95% CI</th><th>Specificity%</th><th>95% CI</th></tr>
<tr><td>Fever</td><td>25/47</td><td>53.2</td><td>53.2</td><td>38.2–67.6</td><td>40</td><td>20–63.6</td></tr>
<tr><td>Hypoactivity or irritability</td><td>26/38</td><td>55.3</td><td>68.4</td><td>51.2–82</td><td>55.6</td><td>31.3–77.6</td></tr>
<tr><td>Prostration</td><td>24/33</td><td>51</td><td>72.7</td><td>54.2–86.1</td><td>55.0</td><td>32–76.2</td></tr>
<tr><td>Coughing</td><td>31/47</td><td>66</td><td>66</td><td>50.6–78.7</td><td>38.1</td><td>19.0–61.3</td></tr>
<tr><td>Dyspnoea (reported)</td><td>32/47</td><td>68.1</td><td>68.1</td><td>52.7–80.5</td><td>47.6</td><td>26.4–69.7</td></tr>
<tr><td>Altered RR (auscultation)</td><td>42/46</td><td>89.3</td><td>91.3</td><td>78.3–97.2</td><td>10.5</td><td>1.8–34.5</td></tr>
<tr><td>RR ≥50rimp</td><td>36/47</td><td>76.6</td><td>76.6</td><td>61.1–87.2</td><td>38.1</td><td>19.0–61.3</td></tr>
<tr><td>RR ≥60rimp</td><td>26/47</td><td>55.3</td><td>55.3</td><td>40.2–69.5</td><td>66.7</td><td>43.1–84.5</td></tr>
<tr><td>Chest indrawing</td><td>21/45</td><td>44.7</td><td>46.7</td><td>31.9–62.0</td><td>80.0</td><td>51.4–94.7</td></tr>
<tr><td colspan="7">N/T: no of cases/total no.</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>The children, who ranged in age from zero to 6 months, had signs and symptoms of acute respiratory infection (ARI), with suspected acute pneumonia and consequently were submitted to chest radiography.

The total number of children from 0 to 12 years old attended at the Emergency Service during the 12-month period was 9,711. Using random sampling, 1,648 bulletins were selected. These included 113 ARI patients from zero to 6 months old, among which 76 had pneumonia. Eighteen paediatricians who had received training in the IRA Program of the MS up to 6 months before were available for data collection.

The respiratory rate (RR) was measured with a chronometer, by observation of the thoracic chest movements or by auscultation of the respiratory sounds with a stethoscope for one minute. The values of respiratory incursions per minute (ripm) were categorized according to World Health Organization (WHO) guidelines for the diagnosis of pneumonia in this age range: The pulmonary auscultation was considered abnormal whenever</td><td>Table :findings in infants 0–6 months with viral pneumonia

<table>
<tr><th>Feature</th><th>N/T</th><th>%</th><th>Sensitivity%</th><th>95% CI</th><th>Specificity%</th><th>95% CI</th></tr>
<tr><td>Fever</td><td>11/29</td><td>37.9</td><td>37.9</td><td>21.3–57.6</td><td>40.0</td><td>20.0–63.6</td></tr>
<tr><td>Hypoactivity or irritability</td><td>16/24</td><td>62.0</td><td>66.7</td><td>44.7–83.6</td><td>55.6</td><td>31.3–77.6</td></tr>
<tr><td>Prostration</td><td>13/19</td><td>44.8</td><td>66.7</td><td>44.7–83.6</td><td>55.6</td><td>31.3–77.6</td></tr>
<tr><td>Coughing</td><td>20/29</td><td>69.0</td><td>69.0</td><td>49.0–84.0</td><td>38.1</td><td>19.0–61.3</td></tr>
<tr><td>Dyspnoea (reported)</td><td>21/29</td><td>72.4</td><td>72.4</td><td>52.5–86.6</td><td>47.6</td><td>26.4–69.7</td></tr>
<tr><td>Altered RR (auscultation)</td><td>24/28</td><td>89.6</td><td>85.7</td><td>66.4–95.3</td><td>10.5</td><td>1.8–34.5</td></tr>
<tr><td>RR> = 50rimp</td><td>25/29</td><td>86.2</td><td>86.2</td><td>67.4–95.5</td><td>38.1</td><td>19.0–61.3</td></tr>
<tr><td>RR> = 60rimp</td><td>20/29</td><td>69</td><td>69</td><td>49.0–84.0</td><td>66.7</td><td>43.1–84.5</td></tr>
<tr><td>Chest indrawing</td><td>13/29</td><td>44.8</td><td>44.8</td><td>27.0–64.0</td><td>80.0</td><td>51.4–94.7</td></tr>
<tr><td colspan="7">N/T: no of cases/total no.

Reported data are not sufficient to check the correctness of the reported figure, PPVs and NPVs are not reported.</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>that there was reduction or abolition of the vesicular murmur, coarse crackles, fine crackles, rhonchi, wheezing, or associations of some of these noises.

X-ray analysis allowed categorization into normal and abnormal. Abnormality was designated when any of the following images was presented: homogeneous or heterogeneous opacity, interstitial infiltrate, hyperinflation or pleural effusion. Normal was when no alteration was displayed. Radiological findings with no relation to the respiratory tract were not necessarily considered as abnormalities.</td><td></td></tr>
<tr><td>Brogan[287]

<u>Study type:</u>

Retrospective and prospective audit.

EL:3</td><td><u>Country:</u>

UK

<u>Condition</u>

Bacterial sepsis.

<u>Aim:</u>

To identify risk factors predictive of significant bacterial sepsis (SBS) in children with fever and petechiae, and to establish a set of clinical guidelines to aid the management of this patient</td><td>Fifty five patients (median age 2.52 years, range 0.22–15.82) satisfying entry criteria presented during the audit periods (November 1997 through April 1998; July 1998 through January 1999). Five of these patients (9%) had SBS.

Table : Clinical and laboratory features of patients identified with significant bacteraemia

<table>
<tr><th>Age (y)</th><th>Sex</th><th>Month of presentation</th><th>Clinical features</th><th>Rash</th><th>Temp.</th><th>WCC (× 10^9/l)</th><th>CRP (mg/l)</th><th>Organism isolated</th><th>Method of detection</th></tr>
<tr><td>13.4</td><td>F</td><td>February</td><td>Toxic and shocked</td><td>Purpuric (initially petechial)</td><td>38 °C</td><td>5.3</td><td>79</td><td>N. meningitidis</td><td>+ blood culture; + rapid Ag</td></tr>
<tr><td>12.8</td><td>M</td><td>February</td><td>Toxic and meningism, received</td><td>Petechial</td><td>40 °C</td><td>24.5</td><td>302</td><td>Group B streptococcus</td><td>+ rapid Ag; −− blood culture (post</td></tr>
</table>
</td></tr>
</table>

Citation/EL	Methodology	Results

group.

Setting, inclusion/exclusion:

Retrospective and prospective audit of referrals to the Paediatric Assessment Unit at The Queen Elizabeth II Hospital, Welwyn Garden City was performed. Patients with peripheral temperature above 37.4 °C, and who had petechial rash (pinpoint bruising of the skin < 2 mm) were eligible for inclusion in the audit. Proposed risk factors for the prediction of SBS were shock (capillary refill time greater than 2 seconds and/or hypotension); irritability (inconsolable crying or screaming); lethargy (as determined subjectively by the carer, nursing, or medical staff); abnormality of the peripheral blood white cell count (WCC) (total WCC outside the range 5–15 × 10^9/l); elevation of C reactive protein (CRP greater than 5 mg/l).

A 'well' patient was defined as a patient who did not manifest any of the proposed risk factors for SBS. An 'unwell' patient was defined as a patient manifesting one or more risk factors for SBS. Culture negative sepsis was defined as patients who appeared clinically toxic, but in whom no organism was

			IM BP						IM BP)
1.46	M	August	Not toxic	Petechial	40.4 °C	22.7	50	*S. pneumoniae*	+ blood culture
12.9	M	January	Toxic	Petechial	38.9 °C	16.8	277	*N. meningitidis* type C	+ PCR; + blood culture
1.52	F	January	Toxic	Purpuric (initially petechial)	40.4 °C	15.2	45	*N. meningitidis* type B	+ PCR; −− blood culture

IM BP, intramuscular benzylpenicillin; PCR, polymerase chain reaction; +, positive; -, negative; Temp., temperature; Ag, antigen; WCC, white cell count; CRP, c-reactive protein.

The performance of the combined risk factors as a screening test for the prediction of SBS based only on those patients who had blood cultures performed (n = 33) were as follows: sensitivity 100% (95% CI, 48–100%); specificity 57% 95% CI, 37–76%); positive predictive value 29% (95% CI, 4–45%); negative predictive value 100% (95% CI, 79–100%); relative risk was unable to obtain due to 100% NPV.

The results based on all patients (n = 55) assuming that those patients who did not have blood cultures performed did not have SBS (no patient died and no patient returned to hospital) were: sensitivity 100% (95% CI, 48–100%); specificity 60% (95% CI, 45–74%); positive predictive value 20% (95% CI, 91–31%); negative predictive value 100% (95% CI, 88–100%); relative risk was unable to obtain due to 100% NPV.

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>isolated.</td><td></td></tr>
<tr><td>Kennedy[138]

Study type:
Retrospective chart review
EL:3</td><td>Country
UK (Scotland)
Condition:
HSE
Aim:
To present the clinical feature of children with HSE.
Methods, inclusion/exclusion:
This is a retrospective analysis and the clinical data presented have been abstracted from the hospital case notes of patients who were diagnosed as having HSE between 1962 to 1985. in all cases the diagnosis had been established by the isolation of herpes simplex virus in tissue culture from brain biopsy tissue and/or autopsy brain tissue.</td><td>A total of 46 patients with definite HSE were identified in the Institute of Neurological Sciences, Glasgow. The age ranged from 1.3 to 71 years.
The protean presenting symptoms and signs included a history of a prodromal influenza-like illness (48 %), rapid onset of headache, clouding of consciousness and confusion (52 %), meningism (65 %), raised intracranial pressure (33%), deep coma (35%), mutism or aphasia (46 %), focal neurological signs (89 %), and seizures (61 %). When seizures occurred they were almost always focal. The electroencephalogram was the most useful diagnostic test being abnormal in all cases, the majority showing focal changes in one or other hemisphere. Of the neuroradiological procedures employed, computerized tomographic and isotope brain scanning most frequently demonstrated localizing abnormalities in one or both temporal and/or frontal lobes. Midline shift was seen in half the cases. The cerebrospinal fluid was abnormal in every case but was not diagnostic. Cerebral biopsy of one temporal lobe was performed in 40 cases and a positive diagnosis of acute necrotizing encephalitis was made in 37 of these. Herpes simplex virus was isolated from the brains of 29 of the 40 cases in which the procedure was attempted, but immunofluorescence assays for antigens to herpes simplex virus were only positive in 11 out of 25 cases. Serological assays showed a greater than four-fold rise in the anti-herpes simplex virus antibody titre in 13 out of 22 patients tested.</td></tr>
<tr><td>Kocher[145]

Study type:
Prospective validation study.
EL:2+</td><td>Country:
US.
Condition
Septic arthritis
Aim:
To validate a previously published clinical prediction rule to differentiate septic arthritis and transient synovitis.</td><td>Of the 51 patients with septic arthritis, 24 (47%) had positive culture; and 16 of them had positive joint-fluid culture and blood culture; six had positive joint-fluid culture and negative blood culture, and two had both negative.
The four independent predictors of septic arthritis of the hip (a history of fever, non-weight-bearing, an erythrocyte sedimentation rate (ESR) of 40 mm/hr, and a serum WBC count of > 12,000 cells/mm3 (> 12.0 x 10^9/L) were identified in the validation patient
population.
Table : Multivariate analysis: septic arthritis with transient synovitis*
<table>
<tr><th></th><th>Adjusted odds ratio</th><th>95% CI</th></tr>
<tr><td>history of fever</td><td>4.4</td><td>1.8–10.4</td></tr>
<tr><td>non-weight-bearing</td><td>5.9</td><td>2.2–16.1</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>Setting, inclusion/exclusion

The authors prospectively studied children who presented to a major children's hospital between 1997 and 2002 with an acutely irritable hip. As in the previous study, diagnoses of septic

arthritis 41 patients) and transient synovitis (103 patients) were

operationally defined on the basis of the white blood-cell count in the joint fluid, the results of cultures of joint fluid and blood, and the clinical

course. Univariate analysis and multiple logistic regression were used to

compare the two groups. The predicted probability of septic arthritis of the hip

from the prediction rule was compared with actual distributions in the current

patient population. The area under the receiver operating characteristic curve

was determined.</td><td>
<table>
<tr><td>ESR = 40 mm/hr</td><td>4.5</td><td>1.8–10.9</td></tr>
<tr><td>Serum WBC count of > 12.0 x 10^9/L</td><td>4.1</td><td>1.7–10.0</td></tr>
</table>
Table : The sensitivity and false positives of for the original and validation studies of septic arthritis
<table>
<tr><td></td><td colspan="2">Derivation</td><td colspan="2">Validation</td></tr>
<tr><td>Cut point</td><td>Sensitivity % (n = 82)</td><td>False-positive rate (n = 86)</td><td>Sensitivity % (n = 51)</td><td>False-positive rate (n = 103)</td></tr>
<tr><td>At least 1 predictor</td><td>100</td><td>0.78</td><td>100</td><td>0.74</td></tr>
<tr><td>At least 2 predictors</td><td>99</td><td>0.23</td><td>90</td><td>0.32</td></tr>
<tr><td>At least 3 predictors</td><td>84</td><td>0.05</td><td>59</td><td>0.11</td></tr>
<tr><td>At least 4 predictor</td><td>31</td><td>0.00</td><td>16</td><td>0.01</td></tr>
<tr><td colspan="5">*: The predictors include a history of fever, non-weight-bearing, an erythrocyte sedimentation rate (ESR) of 40 mm/hr, and a serum WBC count of > 12,000 cells/mm3 (> 12.0 x 10^9/L).</td></tr>
</table>

The predicted probability of septic arthritis of the hip from the prediction rule was similar to the actual distributions in the current patient population. The area under the receiver operating characteristic curve for the current patient population was 0.86, compared with 0.96 in the original population, which indicate good diagnostic performance.</td></tr>
<tr><td>Kao[146]</td><td>Country:

Taiwan</td><td>Eighty-four patients with septic arthritis and 39 with acute haematogenous osteomyelitis were enrolled. Their age ranged from 13 days to 17 years. In patients with septic arthritis, the hip joint (n = 45, 48%) was the most often infected site and followed by knee (n = 28, 31%). The tibia (n = 16, 36% and femur (n = 10, 22%) were the most often involved site in acute haematogenous</td></tr>
</table>

Citation/EL	Methodology	Results
Study type: Retrospective chart review EL 3	Condition: Acute haematogenous osteomyelitis (AHO) & septic arthritis Aim: To analyse the clinical, bacteriological, and radiological features of paediatric patients with acute haematogenous osteomyelitis and septic arthritis. Setting, inclusion/exclusion: The medical chart of 231paediatric patens with a discharge diagnosis of AOH, septic arthritis or both, treated from CG hospital from January 1900 to December 2000 were reviewed. The age of patients ranged from 13 days to 18 years. A total of 123 patients remained in the study after exclusion of patients with traumatic wounds or insufficient evidence to confirm the diagnosis of AHO or septic arthritis.	osteomyelitis. Fifty (91%) of the 123 patients had an elevated ESR and 94 (88%) had an elevated CRP (no further details reported). On admission, patients with septic arthritis had significantly higher ESR than whose with AHO , with median of 75 mm/h (ranged from 1–125 mm/h) and 35 mm/h (ranged from 2–85 mm/h)., respectively (P< 0.005). there is no significant difference between septic arthritis and AHO (P = 0.27). A bacteriological diagnosis was established in 78 (63%) patients. Overall, methicillin-susceptible *Staphylococcus aureus* (36 cases) was the most common causative organism identified, followed by methicillin-resistant *S. aureus* (10 cases). The median duration of antibiotic therapy was 33 days. Serum bactericidal titres were obtained for 19 (15%) of the 123 patients. The median duration of hospitalization and antibiotic treatment was not significantly different between patients with and without serum bactericidal titre testing. More patients without serum bactericidal titre testing had symptom relapse which required re-admission for further treatment.
Razak[147] study type:	Country: Malaysia Condition: Osteomyelitis	They recruited 48 males and 23 females. Majority of them were aged 2–3 years. Sixty percent had a chief complaint of pain (swelling: 20%, failure to use the extremity: 16%,fever: 80% and limp: 8%). Majority of the patient (70%) presented within a week of symptom and significant number of them came with fever (60%, n = 48 had temperature 37.5–39.0 °C; and 20%, n = 17 had > 39.0 °C) and swelling of the affected limb. Sedimentation rate was found to be raised in all of them. Fifty-four (55%) of them were treated surgically. The average antibiotic time was one week by intravenous

Citation/EL	Methodology	Results
retrospective chart review EL: 3	Aim To establish current pattern of clinical presentation, modes of treatment and success of therapy. Setting, inclusion/exclusion: This is a retrospective study with 81 children with AHO who were admitted to a University hospital. The criteria for the diagnosis being the clinical features of AHO: bone tenderness with elevated temperature, and elevated ESR with one or more of the following: (1) operative findings of bone infection; (2) positive bacteriology from aspiration and blood culture and (3) specific radiological or bone scan changes.	administration followed by additional oral therapy for period up to 4 weeks. Average follow-up was 9 months. Six of them (7.5%) end up with various complication which was believed to be due to delay in getting medical treatment.
Akinyoola[148] Study type: retrospective chart review EL: 3	Country: Nigeria Condition: Septic arthritis Method: Clinical and lab reports of patients with septic arthritis from1990–2003 were retrospectively analysed.	The record of 93 patients were eligible. The mean age was 4.5 years (SD 2 months; 2–15 years). the presenting clinical features: joint pain (74.2%), fever (73.1%), and joint swelling (69.9%).
Tseng[149]	Country:	Total of 48 consecutive Kawasaki patients less than 1 year of age were enrolled, which represented 17.5% of the total number of 273 patients with Kawasaki disease in the study period in the study hospital.

Citation/EL	Methodology	Results
   study type: retrospective cohort study EL: 3	Taiwan Condition: Kawasaki diseases Aim: To assess the clinical spectrum of Kawasaki disease in infants. Setting, inclusion/exclusion: Between January 1989 and December 1998,all infants diagnosed with Kawasaki less than 1 year of age were enrolled and studied retrospectively. Typical Kawasaki disease was diagnosed according to the American Heart Association diagnostic criteria established in 1993; including presentation of fever for ≥ 5 days with at least four or five criteria. Coronary artery dilation was defined as the internal diameter of a coronary artery larger than 3 mm. All cases received 2 gm/Kg of intravenous immunoglobulin. They divided the patients into two groups; group I; coronary artery dilation (+) and group II; coronary artery dilation (-), and compared the clinical and laboratory data. Fever was defined as > 38.5 °C measured rectally.	Among these patients (< 1 year old), the median age was 7.8 ± 2.8 months (range 2 months to 12 months), and the male to female ratio was 1.52:1. The incidence of atypical Kawasaki disease was 31.2% (compared with an incidence of atypical Kawasaki disease among patient more than 1 year of age of 7.5%; $P < 0.001$), and that of coronary artery dilation was 35.4%. Clinical manifestations included fever 100%, extremity change 91.6%, skin rash 89.6%, conjunctivitis 89.6%, oral mucosa change 89.6%, and cervical lymphadenopathy 0%. Laboratory data revealed white blood cell count: 15,403 ± 6,282/mm3, haemoglobin: 10.1 ± 1.0 gm/dl, neutrophil: 59.2 ± 13.7%, lymphocytes: 30.6 ± 13.1%, platelet count: 456,3000 ± 216,4000/mm3, and C-reactive protein 8.2 ± 5.6 mg/dl. Patients with coronary artery dilation had a longer duration of diagnosis, higher incidence of atypical presentation, lower incidence of conjunctivitis, lower incidence of skin rash, lower incidence of extremity change, and lower C-reactive protein (all $P< 0.05$). The predictive value of coronary artery dilation based on the combination of atypical presentation, duration of diagnosis, and C-reactive protein was 81.2%.
Huang[150]	Country	A total of 768 patients with Kawasaki disease were reported. The incidence rates of Kawasaki disease for each year were 16.79

Citation/EL	Methodology	Results
Study type: Retrospective questionnaire survey EL: 3	China Condition: Kawasaki diseases Aim: To describe the epidemiology in Shanghai. Setting, inclusion/exclusion A questionnaire form and diagnostic guidelines for Kawasaki disease were sent to hospitals in Shanghai, which provided with paediatric medical care. All patients with Kawasaki disease diagnosed during January 1998 through December 2002 were recruited in this study.	(1998), 25.65 (1999), 28.16 (2000), 28.05 (2001), and 36.76 (2002) per 100,000 children under 5 years of age. The male/female ratio was 1.83:1. The age at onset ranged from 1 month to 18.8 years (median: 1.8 years). The disease occurred more frequently in spring and summer. Persistent fever (n = 736, 99.3%) was the most common clinical symptom, followed by oral and lip changes (n = 641, 83.5%), extremities desquamate (n = 637, 82.9%), rash (n = 622, 81.0%), conjunctive congestion (n = 602, 78.4%), lymphadenopathy (n = 532, 69.3%), extremities swelling (n = 369, 48.1%), and crissum desquamate (n = 347, 45.2%). Cardiac abnormalities were found in 24.3% of patients. The duration of the onset of the first symptom through diagnosis ranged from 1–60 days (average: 10 days). The most common cardiac abnormality was coronary artery lesions including dilatation (68%) and aneurysm (10%). The case-fatality rate at acute stage of the disease was 0.26%. A second onset of the disease occurred in 1.82% of patients.

Heart rate

The predictive values of heart rate of serious illness

Citation/EL	Method	Result
Hanna[111] Study type: Prospective cohort study EL: 2+	Country: US Aim: To evaluate the hypothesis that pulse rate increases linearly with increased body temperature in infants and determine how much tachycardia in infants can be explained by a 1 degrees C (1.8 degrees F) increase in body temperature. Method: Infants younger than 1 year and presenting to a paediatric emergency department were prospectively enrolled. Rectal temperature and pulse rate were measured. Research personnel rated behavioural state as sleeping, awake and quiet, fussy, or crying. Patients were excluded if they were fussy or crying or if they had any medical condition expected to cause tachycardia. The remaining patients were divided into 6 age-based groups. Linear regression analysis of pulse rate and temperature was performed for each group.	Four hundred ninety patients were enrolled. Pulse rate increased linearly with temperature in all age groups older than 2 months (adjusted r2 = 0.102 to 0.376) but not in infants younger than 2 months (adjusted r2 = 0.004). In infants aged 2 months or older, a multivariate linear regression model adjusted for age showed that pulse rate increased an average of 9.6 beats/minute (95% confidence interval 7.7 to 11.5) per 1 degrees C (1.8 degrees F) increase in temperature (adjusted r2 = 0.225). At any given temperature, the prediction interval for an individual's pulse rate had a span of approximately 64 beats/minute.

CRT

Capillary refill time

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Result</th></tr>
<tr>
<td>Leonard[113]

EL:2+

Study type : prospective cohort study.</td>
<td><u>Country :</u>
Scotland.

<u>Aim:</u>
To determine if capillary refill time (CRT) at the time of initial presentation was a useful measure of illness severity in children with a recent onset of illness.

Setting, inclusion/exclusion:
All children (0–12 years) with recent (< 7 days) onset of illness attending a paediatric A&E over a 7-month period were eligible. Children presenting with cardiac arrest and therefore having no spontaneous circulation were excluded. As were those presented as a result of trauma. An experienced paediatric triage nurse assessed all children within 5 minutes of arrival, and allocate the child a subjective triage category of 1 (immediate) to 4 (non-urgent). CRT was measured using a standardised technique. The CRT values were recorded at the whole second.</td>
<td>A total of 6978 children were eligible for the entry. However, only 4878 children (70%) were compliant to the triage nurses. There was no significant difference between the ones who entered and the ones who didn’t (P> 0.05).

Table : Breakdown of diagnosis by age of patient (total number = 4878, only extracted data for those under six).
<table>
<tr><td>Age (years)</td><td>0–2</td><td>2–4</td><td>4–6</td></tr>
<tr><td>Significant bacterial illness*</td><td>133</td><td>57</td><td>34</td></tr>
<tr><td>Minor bacterial illness*</td><td>160</td><td>113</td><td>91</td></tr>
<tr><td>Viral illness</td><td>944</td><td>251</td><td>129</td></tr>
<tr><td>Asthma</td><td>15</td><td>67</td><td>32</td></tr>
<tr><td>Allergy/anaphylaxis</td><td>21</td><td>6</td><td>17</td></tr>
<tr><td>Poisoning</td><td>35</td><td>48</td><td>12</td></tr>
<tr><td>Gastroenteritis</td><td>317</td><td>97</td><td>39</td></tr>
<tr><td>Metabolic disturbance</td><td>9</td><td>3</td><td>4</td></tr>
<tr><td>Seizure</td><td>18</td><td>14</td><td>18</td></tr>
<tr><td>Miscellaneous illness</td><td>453</td><td>244</td><td>167</td></tr>
<tr><td colspan="4">*: not defined.</td></tr>
</table>
There was no significant association of CRT with meningococcal disease, other significant bacterial illness or WBC (statistics not provided).

A prolonged CRT was associated with a more urgent triage category, the administration of fluid bolus and the length of hospital stay.

The ROC curve showed that the best performance was obtained when a CRT of 3 seconds was taken to be as ‘prolonged’.

Table : values of CRT of 3 seconds as a predictor of illness severity.</td>
</tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Result</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Marker</td><td>Sensitivity (95% CI)</td><td>Specificity (95% CI)</td><td>PPV %</td><td>NPV %</td><td>RR</td></tr>
<tr><td>Triage category 1 or 2</td><td>29 (23.6–36.2)</td><td>86 (85.1–87 1)</td><td>9</td><td>96</td><td>2.25</td></tr>
<tr><td>Fluid bolus</td><td>56 (47.5–64.8)</td><td>87 (85.7–87.6)</td><td>11</td><td>99</td><td>11.0</td></tr>
<tr><td>Admitted</td><td>21 (19.2–22.9)</td><td>89 (88.3–90.5)</td><td>55</td><td>65</td><td>1.57</td></tr>
<tr><td>Hospitalisation ≥ 2 days</td><td>28 (24.7–32.5)</td><td>87 (86.2–88.2)</td><td>22</td><td>91</td><td>2.44</td></tr>
</table>
</td></tr>
<tr><td>Gorelick[114]

EL: 2+

<u>Study type:</u>
Prospective cohort study.</td><td><u>Country:</u>
USA
<u>Aim :</u>
To assess the effect of fever on capillary refill time in children.
Setting, inclusion/exclusion:
A convenient sample of children 1 months to 5 years treated in the A&E with the chief complaint of vomiting, diarrhoea, or poor oral fluid intake were included. Children were excluded if they had history of cardiac or autonomic disease, malnutrition or failure to thrive, use of oral decongestants in the prior 24 hr, or treated with IV fluid before arrival. Children with hyponatraemia or hyponatraemia</td><td>There were 276 subjects were initially enrolled. Of the 174 admitted to hospital, seven were excluded. 102 eligible children being discharged from the A&E were enrolled, two refused to participate. Seventy-seven (76%) of the discharged completed the follow-up. Median age was 12.5 months.
Mean temperature among febrile children was 39.2 °C (38.1–41.3 °C). Mean CRT was 1.5 seconds (SD 0.8 seconds). The inter-rater coefficient was 0.72.
There was no significant relationship between CRT and body temperature (r = 0.01, P> 0.5).
At the cut-off of 2 seconds, 35/80 (43.75%) children with dehydration had prolonged capillary refill, with a sensitivity of 44% for predicting a fluid deficient of < 5% or more of body weight.</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Result</th></tr>
<tr><td></td><td>were excluded.

Fever was defined as a temperature ≥38 °C. CRT was measure by 17 experienced nurses. Room temperature was monitored.</td><td></td></tr>
<tr><td>Otieno[115]

<u>Study type:</u>
prospective cohort study

EL: 2+</td><td><u>Country:</u>

Kenya

<u>Aim:</u>

To examine prospectively the inter-observer reproducibility of bedside clinical features of shock. It did not, however, seek to validate the ability of any sign to define shock.

<u>Method, inclusion/exclusion:</u>

The study was conducted at Kilifi District Hospital (KDH) on the coast of Kenya. Detailed descriptions of the facilities and routine clinical assessment of children admitted to KDH. During weekdays from June to July 2003, four clinicians independently assessed consecutive morning admissions to the general paediatric ward. Each clinician had 2–3 years postgraduate clinical experience. All assessments were conducted within one hour of each other. The study clinicians were unaware of each child’s clinical details and admission diagnosis,</td><td>One hundred consecutive paediatric admissions were assessed independently by each of the four clinicians. The study group age ranged from 2 days to 10 years 11 months. Presenting complaints included fever (n = 78), cough (n = 43), respiratory distress (n = 25), diarrhoea and/or vomiting (n = 26), and convulsions (n = 25). Many had poor nutritional status: undernutrition (WAZ score –2 to –3 SD) and severe malnutrition (WAZ score ≤3SD, plus visible severe wasting) were present in 22% and 18% respectively, and seven children had oedematous malnutrition (kwashiorkor).

Table : Categorical definitions of the features assessed by the clinicians

<table>
<tr><td>Feature</td><td>Values</td></tr>
<tr><td>Capillary refill time (seconds)</td><td>1, 2 ,3, 4 or more</td></tr>
<tr><td>Temperature gradient</td><td>Yes, no</td></tr>
<tr><td>Pulse volume</td><td>Weak (or absent), normal, strong/bounding</td></tr>
<tr><td>Decreased skin turgor</td><td>Yes, no</td></tr>
<tr><td>Sunken eyes</td><td>Yes, no</td></tr>
<tr><td>Dry mucous membranes</td><td>Yes, no</td></tr>
</table>

Overall agreement for CRT was moderate (k = 0.42), and was better for normal values (≤1 second) (k = 0.48) and clearly abnormal values (≥4 seconds) (k = 0.49). There was moderate to substantial agreement between observers for temperature gradient, being slightly better for the lower limb (k = 0.62) than the upper limb (k = 0.57). There was moderate agreement in the assessment of weak pulse volume (k = 0.40); however, there was little to no agreement for bounding pulse volume (k = –0.01). In the assessment of hydration status the level of agreement was substantially better for a decreased skin turgor (k = 0.55) than either sunken eyes or dry mucous membranes, for which agreement was only fair (0.34 and 0.39 respectively). There was no significant difference in these findings after stratification for the presence or absence of malnutrition.

Table : Inter-observer agreement between four clinicians in the signs of shock</td></tr>
</table>

Citation/EL	Method	Result
	and categorical definitions and standard methods for eliciting each clinical feature were agreed initially (see table of Categorical definitions of the features assessed by the clinicians). Capillary refill time (CRT) was assessed by applying pressure to a finger pulp for three seconds and counting the time required for the blanched finger to fully re-perfuse. Temperature gradient was assessed by running the back of the palm of the hand down the limb and reported for both the upper and lower limbs. The radial pulse was used to assess pulse volume. Reduced skin turgor was assessed by pinching a longitudinal skin fold midway between the umbilicus and the flank (as recommended by the WHO Integrated Management of Childhood Illness (IMCI) guidelines) and observing whether the skin pinch goes back slowly. Cohen's kappa statistic (*k*) was used as a measure of agreement.	

Feature	Kappa (*k*)	95% CI
Capillary refill time		
1	0.48	0.34 to 0.62
2	0.37	0.25 to 0.49
3	0.35	0.23 to 0.47
4	0.49	0.35 to 0.63
Combined	0.42	0.29 to 0.55
Temperature gradient		
Upper limb	0.57	0.42 to 0.72
Lower limb	0.62	0.47 to 0.77
Pulse volume		
Weak	0.40	0.28 to 0.52
Normal	0.30	0.19 to 0.41
Strong/bounding	–0.01	
Dehydration		
Dry mucous membranes	0.39	0.27 to 0.51
Decreased skin turgor	0.55	0.40 to 0.70
Sunken eyes	0.34	0.23 to 0.45

Interpretation of kappa statistic:[16]

Below 0, poor agreement

0–0.2, slight

0.2–0.4, fair

0.41–0.6, moderate

0.61–0.8, substantial

0.81–1.0, almost perfect agreement

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Result</th></tr>
<tr>
<td>Tibby[116]

<u>Study type:</u>

EL:2- (ICU population)</td>
<td><u>Country:</u>
UK

<u>Aim:</u>
This study assesses capillary refill time relation to commonly measured haemodynamic parameters in the post-resuscitation phase when the child has reached the intensive care unit, and compares this with core-peripheral temperature gap.

<u>Method, inclusion/exclusion</u> :
Capillary refill time was measured in ventilated patients in whom invasive haemodynamic monitoring was instituted for clinical reasons. Exclusion criteria included conditions that would affect the accuracy of thermodilution measurements of cardiac index, such as anatomical shunts (confirmed by colour Doppler echocardiography), arrhythmias, or valvular regurgitation.

All measurements of capillary refill time were made by the same clinician (ST) in the following manner: the upper limb (not containing an indwelling arterial catheter) was raised slightly above the level of the heart and firm pressure was applied by the clinician’s index finger and thumb to the distal</td>
<td>Ninety measurements were made on 55 patients who were subdivided into two groups: postcardiac surgery (n = 27), and general (n = 28). Twenty four of the 28 patients in group 2 had septic shock; other diagnoses (all n = 1) were: multi-organ failure secondary to hypernatraemic dehydration, hypertrophic cardiomyopathy, nephrotic syndrome with pulmonary oedema, and bilateral subdural effusions associated with an apparent life-threatening event.

For cardiac patients, both capillary refill time and core-peripheral temperature gap correlated poorly with all haemodynamic variables.

Table : Correlation between capillary refill time (CRT), core-peripheral temperature gap, and haemodynamic variables for patients after cardiac surgery and general patients
<table>
<tr><th>Patient group</th><th>Variable</th><th>CRT r (95% CI)</th><th>P value</th><th>Core-peripheral temperature gap r (95% CI)</th><th>P value</th></tr>
<tr><td colspan="6">After cardiac surgery</td></tr>
<tr><td></td><td>CI</td><td>−0.06 (−0.36 to 0.25)</td><td>0.70</td><td>−0.12 (−0.41 to 0.20)</td><td>0.44</td></tr>
<tr><td></td><td>CVP</td><td>−0.14 (−0.43 to 0.17)</td><td>0.35</td><td>−0.18 (−0.46 to 0.14)</td><td>0.26</td></tr>
<tr><td></td><td>SVRI</td><td>0.06 (−0.25 to 0.36)</td><td>0.68</td><td>0.14 (−0.17 to 0.43)</td><td>0.36</td></tr>
<tr><td></td><td>SVI</td><td>−0.09 (−0.39 to 0.22)</td><td>0.54</td><td>−0.19 (−0.47 to 0.12)</td><td>0.22</td></tr>
<tr><td></td><td>Lactate</td><td>0.11 (−0.22 to 0.42)</td><td>0.51</td><td>0.11 (−0.22 to 0.43)</td><td>0.50</td></tr>
<tr><td colspan="6">General</td></tr>
<tr><td></td><td>CI</td><td>−0.21 (−0.47 to 0.08)</td><td>0.13</td><td>−0.24 (−0.52 to 0.08)</td><td>0.13</td></tr>
<tr><td></td><td>CVP</td><td>0.34 (0.04 to 0.58)</td><td>0.02</td><td>0.00 (−0.30 to 0.32)</td><td>0.99</td></tr>
<tr><td></td><td>SVRI</td><td>0.01 (−0.29 to 0.31)</td><td>0.95</td><td>0.29 (−0.04 to 0.55)</td><td>0.08</td></tr>
<tr><td></td><td>SVI</td><td>−0.46 (−0.67 to −0.18)</td><td>0.001</td><td>−0.29 (−0.56 to 0.03)</td><td>0.07</td></tr>
</table>
</td>
</tr>
</table>

Citation/EL	Method	Result
	phalanx of the patients' index finger for five seconds. The finger was then released and the time taken for the palmar pulp to return to its previous colour was recorded. Times were measured to the nearest second by a wristwatch (as is usual in clinical practice). Measurements were not made on overtly ischaemic limbs in patients with meningococcal disease. For postcardiac surgery patients, measurements were made after bypass rewarming was complete, defined as a rectal temperature of ≥ 37°C. All measurements were made in an open, well lit intensive care unit, where the ambient temperature was maintained at 22°C. The median number of capillary refill time measurements for each patient was two. No patient had more than three measurements, and repeat measurements were only taken after a time interval of at least one hour and after a treatment that might alter the haemodynamic profile, such as a fluid bolus or the addition of an inotropic agent. Normal capillary refill was defined as ≤ 2 seconds, and prolonged refill as > 2 seconds.	<table><tr><td></td><td>Lactate</td><td>0.47 (0.21 to 0.66)</td><td>< 0.001</td><td>0.31 (−0.02 to 0.57)</td><td>0.06</td></tr><tr><td colspan="6">CI, cardiac index; CVP, central venous pressure; SVRI, systemic vascular resistance index; SVI, stroke volume index.</td></tr></table> Cardiac patients with normal and prolonged capillary refill time showed no difference with respect to median CI (3.42 *vs.* 2.93 l/minute/m^2; *P* = 0.57), SVI (28 *vs.* 24 ml/m^2; *P* = 0.85), central venous pressure (8 *vs.* 9 mm Hg; *P* = 0.75), SVRI (1476 *vs.* 1474 dyne/s/cm^5/m^2; *P* = 0.42), or lactate (1.4 *vs.* 1.8 mmol/l; *P* = 0.50). Among the non-cardiac patients, capillary refill time and core-peripheral temperature gap also exhibited a close association (*r* = 0.66; 95% CI 0.44 to 0.81; *P* < 0.0001). Overall capillary refill time exhibited a stronger correlation between haemodynamic variables, notably SVI and lactate. Because SVI was the only parameter related consistently to capillary refill time, the predictive value of capillary refill time to pick up a low SVI (less than 30 ml/m^2) was assessed by an ROC curve. The best predictive ability was shown with a capillary refill time of ≥ 6 seconds, giving a sensitivity of 57%, specificity of 94%, positive predictive value of 80%, negative predictive value of 83% and relative risk of 4.7. In contrast, a capillary refill time of ≥ 3 seconds gave a sensitivity of 86%, specificity of 47%, positive predictive value of 41%, negative predictive value of 88% and relative risk of 4.86.

Dehydration

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr>
<td>Steiner[117]

Study type: systematic review

EL 2+

(different population)</td>
<td>Aim:

To systematically review the precision and accuracy of symptoms, signs, and basic laboratory tests for evaluating dehydration in infants and children.

Method:

They identified articles by direct searches of the MEDLINE database via the PubMed search engine. The first and most broad search strategy used dehydration and diagnosis, hypovolemia and diagnosis, or intravascular volume depletion and diagnosis. All were limited by age (all children: 0–18 years) and publication date (January 1966–April 2003). These searches produced 1537 articles. They supplemented this preliminary search with the standardized search technique used in the ‘Rational Clinical Examination’ series (available from the authors). This second search produced 24 additional articles.

Each of the authors reviewed the titles and available abstracts from the 1561 articles, selecting for further review those that appeared to address the evaluation of dehydration in children aged 1 month to 5 years. They did not exclude articles if the study enrolled some children outside of that age range. Through consensus, they identified 68 articles as potential sources of primary data or reviews with potential background information and thorough reference lists.

They performed a full review of the 110 retained articles to identify those with primary data comparing dehydration with a symptom, sign, or laboratory value in paediatric patients. Twenty-six articles met these criteria and underwent full quality assessment using an established methodological filter.</td>
<td>Three studies evaluated the accuracy of history taking in assessing dehydration. All 3 of these studies evaluated history of low urine output as a test for dehydration. In the pooled analysis, low urine output did not increase the likelihood of 5% dehydration (LR, 1.3; 95% CI, 0.9–1.9). Porter et al showed that a history of vomiting, diarrhoea, decreased oral intake, reported low urine output, a previous trial of clear liquids, and having seen another clinician during the illness prior to presenting to the ED yielded LRs that lacked utility in the assessment of dehydration. However, their data did suggest that children who had not been previously evaluated by a physician during the illness might be less likely to be dehydrated on presentation (LR, 0.09; 95% CI, 0.01–1.37). Similarly, parental report of a normal urine output decreases the likelihood of dehydration (Gorelick et al reported an LR of 0.27 [95% CI, 0.14–0.51] and Porter et al reported an LR of 0.16 [95% CI, 0.01–2.53]).

Table : Summary characteristics for clinical findings to detect 5% dehydration.
<table>
<tr><th></th><th></th><th colspan="2">LR summary,
Value (95 °CI) or range</th><th></th><th></th></tr>
<tr><th>Finding</th><th>Total No.</th><th>Present</th><th>Absent</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr>
<tr><td>Prolonged CRT</td><td>478</td><td>4.1 (1.7–9.8)</td><td>0.57 (0.39–0.82)</td><td>0.60 (0.29–0.91)</td><td>0.85 (0.72–0.98)</td></tr>
<tr><td>Abnormal skin turgor</td><td>602</td><td>2.5 (1.5–4.2)</td><td>0.66 (0.57–0.75)</td><td>0.58 (0.40–0.75)</td><td>0.76(0.59–0.93)</td></tr>
<tr><td>Abnormal respiratory pattern</td><td>581</td><td>2.0 (1.5–2.7)</td><td>0.76 (0.62–0.88)</td><td>0.43 (0.31–0.55)</td><td>0.79(0.72–0.86)</td></tr>
<tr><td>Sunken eyes</td><td>533</td><td>1.7 (1.1–2.5)</td><td>0.49 (0.38–0.63)</td><td>0.75 (0.62–0.88)</td><td>0.52 (0.22–0.81)</td></tr>
<tr><td>Dry mucus membranes</td><td>533</td><td>1.7 (1.1–2.6)</td><td>0.41 (0.21–</td><td>0.86 (0.80–0.92)</td><td>0.44 (0.13–0.74)</td></tr>
</table>
</td>
</tr>
</table>

Citation/EL	Method	Results
	To ensure a comprehensive literature review, they used additional techniques to identify articles. One author (M.J.S.) searched for individual symptoms and signs associated with the diagnosis of dehydration in children. These terms included *capillary refill*, *skin turgor*, *dry cry*, *tears*, *mucous membrane*, *sunken eyes*, *fontanelle* and *dehydration*, *urine specific gravity*, *urine* and *dehydration*, *haemoconcentration*, *BUN*, *urine*, *blood pressure*, *bioimpedance*, *orthostasis*, *respiration*, *parent* and *dehydration*, *pulse*, and *heart rate* (all limit: aged 0–18 years, human, NOT *dehydration* and *diagnosis*). The Cochrane Library, reference lists of paediatric and physical examination textbooks, reference lists of all included articles, and articles from the collections of experts in the field were reviewed. Forty-two potential articles were identified from the supplemental searches. A second author then checked the initial quality review. The group always arrived at a consensus on the final evidence quality level assigned. Nine of the 110 articles that underwent a full text review were written in languages other than English. Medical school faculty, residents, or students at our institution who were primary speakers of the written language read each of these articles. Six of these 9 articles did not meet inclusion criteria and were excluded, while 3 were assigned an evidence quality level based on a translation of the article. No studies on physical examination signs, symptoms, or laboratory results in childhood dehydration demonstrated evidence quality criteria for level 1 or 2. Four studies were assigned to level 3, but 1 of these was eventually excluded because the study population overlapped with that in another included study. Twelve studies were initially assigned to level 4, though 1 was excluded because of methodological flaws and another was excluded because of its retrospective design and restriction to children with pyloric stenosis.	<table><tr><td></td><td></td><td></td><td>0.79)</td><td></td><td></td></tr><tr><td>Cool extremity</td><td>206</td><td>1.5,18.8</td><td>0.89–0.97</td><td>0.10, 0.11</td><td>0.93, 1.00</td></tr><tr><td>Week pulse</td><td>360</td><td>3.1, 7.2</td><td>0.66–0.96</td><td>0.04, 0.25</td><td>0.86, 1.00</td></tr><tr><td>Absent tears</td><td>398</td><td>2.3 (0.9–5.8)</td><td>0.54 (0.26–1.13)</td><td>0.63 (0.42–0.84)</td><td>0.68 (0.43–0.94)</td></tr><tr><td>Increased heart rate</td><td>462</td><td>1.3 (0.8–2.0)</td><td>0.82 (0.64–1.05)</td><td>0.52 (0.44–0.60)</td><td>0.58 (0.33–0.82)</td></tr><tr><td>Sunken fontanelle</td><td>308</td><td>0.9 (0.6–1.3)</td><td>1.12 (0.82–1.54)</td><td>0.49 (0.37–0.60)</td><td>0.54 (0.22–0.87)</td></tr><tr><td>Poor overall appearance</td><td>398</td><td>1.9 (0.97–3.8)</td><td>0.46 (0.34–0.61)</td><td>0.80 (0.57–1.04)</td><td>0.45 (−0.1 to 1.02)</td></tr><tr><td colspan="6">LR: likelihood ratio.</td></tr></table> Three signs were evaluated in multiple studies, had a clinically helpful pooled LR in detecting 5% dehydration, and had 95% CIs wholly above 1.0. Capillary refill time was evaluated in 4 different studies, and the pooled sensitivity of prolonged capillary refill time was 0.60 (95% CI, 0.29–0.91), with a specificity of 0.85 (95% CI, 0.72–0.98), for detecting 5% dehydration. The LR for abnormal capillary refill time was 4.1 (95% CI, 1.7–9.8). This was the highest value among examination signs with pooled results. Abnormal skin turgor had a pooled LR of 2.5 (95% CI, 1.5–4.2) and abnormal respiratory pattern had a pooled LR of 2.0 (95% CI, 1.5–2.7). Presence of cool extremities or a weak pulse or absence of tears also may be helpful tests for dehydration. Absence of tears had a pooled LR of 2.3 (95% CI, 0.9–5.8), but the potential utility is limited by a wide 95% CI that crosses 1.0. Two studies examined a weak pulse quality as a test for dehydration. One study found a reasonably precise LR for weak pulse of 3.1 (95% CI, 1.8–5.4), but in the other study, the 95% CI was too wide to make a reasonable estimate (LR, 7.2; 95% CI, 0.4–150). The 2 studies that evaluated cool extremities as a test of dehydration found imprecise point estimates for the LR positive in detecting 5% dehydration (LR, 18.8; 95% CI, 1.1–330and LR, 1.5; 95% CI, 0.2–12).

Citation/EL	Method	Results
	They chose the difference between the rehydration weight and the acute weight divided by the rehydration weight as the best available gold standard of percentage of volume lost. Ten articles used gold standards based solely on examination signs or a general dehydration assessment. These were assigned an evidence quality level of 5 and were subsequently excluded.	Sunken eyes and dry mucous membranes offer little help clinically; both had narrow 95% CIs but pooled LRs of 1.7. An increased heart rate, a sunken fontanelle in young infants, and an overall poor appearance are frequently taught as good tests for dehydration. However, the objective evidence reveals that all have summary LRs of less than 2.0 and 95% CIs that cross 1.0. Some tests may be clinically useful in decreasing the likelihood of dehydration. Absence of dry mucous membranes (LR, 0.41; 95% CI, 0.21–0.79), a normal overall appearance (LR, 0.46; 95% CI, 0.34–0.61), and absence of sunken eyes (LR, 0.49; 95% CI, 0.38–0.63) had pooled LRs of less than 0.5. Most clinical scenarios will necessitate lower LRs than these to rule out dehydration effectively.

Chest X- ray (CXR)

Citation/EL	Methodology	Effect size
Swingler[152] EL: 1+	Study type: Systematic review Aim: To assess the effects of chest radiography for children with acute lower respiratory infections. Search strategy The searches were updated in November 2004. They searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2005), MEDLINE (1966 to February, Week 1 2005) and EMBASE (January 1990 to September 2004). They contacted experts in the fields of acute respiratory infections and paediatric radiology to locate additional studies. Selection criteria Randomised or quasi-randomised trials of chest radiography in children with acute respiratory infections. Data collection and analysis One reviewer extracted data and assessed trial quality.	Types of participants Trials were limited to those involving children under the age of 18 years or which separately reported data on subgroups of children under 18 years. Participants must have had a clinical diagnosis of respiratory infection or a clinical case definition consistent with a diagnosis of respiratory infection. Participants must have had symptoms for 21 days or less at the time of the first chest x-ray. Types of intervention The intervention was the use of chest radiography (antero-posterior film with or without a lateral film), compared with the use of clinical judgment without radiography. Types of outcome measures The principal outcome was resolution of symptoms, expressed either as time from randomisation to recovery or as the proportion of cases recovered after a specific interval. Secondary outcome measures were: a) the proportion of cases making subsequent visits to a healthcare provider within 4 weeks; b) the proportion of cases subsequently admitted to hospital within 4 weeks; c) all cause mortality within 4 weeks. Results Two trials of chest radiography in acute respiratory infections were identified. One was excluded because the participants were adults. The single eligible trial was limited to ambulatory children and was performed in the primary-level outpatients section of a children's hospital in Cape Town, South Africa. The 522 participants were aged 2 to 59 months and met the WHO clinical case definition for 'pneumonia', which the WHO recommends to be managed at home with antibiotics. Children with symptoms for longer than 14 days or with a household contact with active tuberculosis were excluded. Use of chest radiograph was compared with management without a radiograph. All other patient management was at the discretion of the clinician. Outcomes measured were time to recovery and subsequent hospital visits and hospital admission occurring within 4 weeks. Hospital visits and admissions were measured from hospital records. Time to recovery was measured by twice-weekly telephone interviews in the subset of participants who offered a contact telephone number. **Methodological quality**

Citation/EL	Methodology	Effect size
		The trial had a low risk of bias, except for incomplete follow up with respect to the primary outcome. Treatment allocation was randomised and was concealed by using sealed sequentially numbered envelopes. Follow up of the primary outcome was achieved in 77.5% of participants. This opens the possibility of bias from loss to follow up though the loss was numerically similar between treatment groups. The finding of no effect of radiography in both the primary outcome (where telephone follow up was incomplete) and in secondary outcomes (when follow up of hospital records was virtually complete) reduces but does not exclude the probability of attrition bias. Assessment of the primary outcome, but not of the secondary outcomes, was performed without knowledge of the treatment group. The above comments must be considered in the light of the fact that the authors of this review are also the authors of that trial. **Results** Forty-six per cent of both radiography and control participants had recovered by seven days. The odds ratio (OR) was 1.03 (95% confidence interval (CI) 0.64 to 1.64). The odds ratios for remaining ill at four and 14 days were 0.74 (95% CI 0.45 to 1.23) and 0.82 (95% CI 0.45 to 1.48) respectively. Thirty-three per cent of radiography participants and 32% of control participants made a subsequent hospital visit within 4 weeks (OR 1.02, 95% CI 0.71 to 1.48). Three per cent of both radiography and control participants were subsequently admitted to hospital within 4 weeks (OR 1.02, 95% CI 0.40 to 2.60). There were no deaths in either group. The trial was performed in a single hospital outpatients department, and 47 of the 52 clinicians were general medical practitioners. The planned subgroup analyses by level of health facility and category of health worker were thus not performed.
Swingler[262] EL:1+	Study type: RCT Aim: To quantify the effect of the use of chest radiographs on management and clinical outcome in children with ambulatory acute lower-respiratory infection, and to determine whether any such effect was dependent on the experience of the clinician.	Of the 581 eligible patients identified by the registered nurse, 59 (26 contactable by telephone) were excluded by the clinicians before randomisation. The remaining 522 patients were randomly allocated, 259 to the radiograph group and 263 to the control group. Four (1·5%) patients in the radiograph group did not receive the intervention whereas 7 (2·7%) of the control group had a radiograph on the day of randomisation. Details of follow-up showed 295 (77·5%) of the patients providing a telephone number were followed till recovery or censored at 28 days. Of the 522 participants 518 (99·2%) record sheets of the first consultation were retrieved, and all 522 folders for assessment of subsequent visits. The median time to recovery was 7 days for both groups (95% CI 6–8 days in the radiograph group and 6–9 in the control group, $P = 0{\cdot}50$, log-rank test). No deaths were recorded. With Cox proportional-hazards regression the unadjusted hazard ratio for recovery for the radiograph group compared with the control group was 1·08 (CI 0·85–1·34). The hazard ratio was not changed by adjustment for age, weight for age, duration of symptoms before presentation, respiratory rate, postgraduate paediatric

Citation/EL	Methodology	Effect size
	Country: S. Africa Subjects, inclusion/exclusion: 522 children aged 2 to 59 months who presented to the Red Cross Children's Hospital as their first contact were eligible for this study and met the WHO case definition for pneumonia were randomly allocated to have a chest radiograph or not. The main outcome was time to recovery, measured in a subset of 295 patients contactable by telephone. Subsidiary outcomes included diagnosis, management, and subsequent use of health facilities. Intervention Eligible patients identified by the nurse were seen by a clinician. After the medical history of each patient was taken and an examination done, eligible patients were allocated to the radiograph or to the control group. Allocation was done by the clinician opening a sealed sequentially numbered manila envelope attached to the consultation sheet and containing the random allocation generated in advance by the principal investigator (by tossing a coin). If a patient was excluded by the clinician before randomisation the sealed envelope was returned to the principal investigator. The intervention was the use of a chest radiograph (anteroposterior and lateral views). The chest radiograph was viewed by the clinician and a routine report	qualification being held by the clinician, clinicians' time spent working in the outpatients department, and clinicians' perception of the need for chest radiograph (1·08 CI 0·84–1·38). There were no significant interactions of the above factors with chest radiograph use. In the subgroup of patients perceived by clinicians to need a chest radiograph the hazard ratio for recovery was 0·91 (CI 0·52–1·60). More radiograph patients were diagnosed as having pneumonia or upper-respiratory infection, while a higher proportion of control patients were diagnosed as having bronchiolitis (both $P< 0.05$). While 149 (60·8%) of 245 children in the radiograph group received antibiotics only 133 (52·2%) of 255 children in the control group did ($P = 0·05$). There were trends towards a higher proportion of radiographed patients receiving follow-up appointments and being admitted to hospital, but these were not significant ($P = 0·08$ and $P = 0·14$, respectively). No differences were found in subsequent consultations, hospital admissions, and chest radiographs done within 28 days. k scores for agreement between telephone interview and examination of the clinical records were 0·88, 0·81, and 0·58, respectively, for subsequent visits, hospital admission, and chest radiographs. Of the 12 items assessed for inter-observer agreement in the record review, k scores were 1·0 for six items, above 0·9 in another two, and above 0·8 in a further three. The only k score below 0·8 was 0·60 for diagnosis.

Citation/EL	Methodology	Effect size
	supplied by the duty paediatric radiologist or radiology registrar was available with the films. The control was standard care without a chest radiograph.	

Oximetry

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr>
<td>Duke[263]

<u>Study type:</u>
Prospective cohort study

EL : II

(SpO_2): transcutaneous oxygen saturation ;
Acute lower respiratory infections (ALRI)</td>
<td><u>Country:</u>
Eastern Highlands of Papua New Guinea
<u>Aim:</u>
To determine, in sick neonates and children requiring admission to a hospital in the highlands of Papua New Guinea: (1) the incidence and severity of hypoxaemia; (2) the proportion with hypoxaemia who do not fulfil criteria for acute lower respiratory infection (ALRI); and (3) the power of clinical signs to predict hypoxaemia, according to age and disease category.
<u>Setting, inclusion/exclusion:</u>
This study was done at Goroka Hospital, a base hospital in the Eastern Highlands of Papua New Guinea located at an altitude of 1600 m above sea level. The hospital serves a mixed rural and periurban population.
To establish normal values of haemoglobin oxygen saturation, children from 1 month to 5 years were recruited from the outpatient immunisation clinic, and neonates (28 days of age or less) were recruited from the postnatal ward. They were eligible if they were assessed as being healthy, based on history and examination. SpO_2</td>
<td><u>Normal values of haemoglobin oxygen saturation</u>
A total of 218 well children were studied: 67 neonates (aged < 28 days) and 151 older children (1–60 months). The overall mean and median SpO_2 were 95.0% (range 75–100%). The mean SpO_2 for children was lower for neonates than older children: 93.3% (SD 3.4%) compared with 95.7% (SD 2.7%) (P < 0.0001).
To determine the proportion of children in age and diagnostic groups with hypoxaemia,
They defined hypoxaemia as SpO_2 more than 2SD below the mean for age. For neonates this value was 86.5%, so hypoxaemia was considered to be present if the SpO_2 was less than 86%. In older children this value was 90.3 and hypoxaemia was considered to be present if the SpO_2 was less than 88%.
<u>Hypoxaemia in sick children and neonates with and without ALRI</u>
A total of 491 sick children were evaluated: 132 neonates and 359 between 1 month and 5 years.
Of 245 patients with ALRI, 179 (73%) had hypoxaemia. In addition, 79 (32%) of the 246 patients who did not fulfil criteria for ALRI illnesses were hypoxaemic. Of the 136 (28%) children 1 month to 5 years who did not fulfil criteria for ALRI, 38 (28%) were hypoxaemic. Outside the neonatal period, common non-ALRI conditions associated with hypoxaemia were meningitis, septicaemia, and severe malnutrition. Although many children with these diagnoses also fulfilled the criteria for ALRI, and probably had pneumonia as a co-infection, these 38 children between 1 month and 5 years with hypoxaemia had no evidence of associated ALRI.
Table : ALRI, non-ALRI and diagnostic specific oxygen saturation in children aged 1 month to 5 years.
<table>
<tr><th>Principal diagnosis</th><th>No.</th><th>Median (IQR) SpO_2</th><th>Number (%) with clinical ALRI</th><th>% with SpO_2< 88%</th><th>P value</th></tr>
<tr><td>Normal children</td><td>151</td><td>96 (95–97)</td><td>0</td><td>3 (2)</td><td></td></tr>
<tr><td>All sick children</td><td>359</td><td>86 (76–93)</td><td>223 (62)</td><td>200 (56)</td><td>< 0.0001</td></tr>
<tr><td>ALRI</td><td>223</td><td>82 (72–88)</td><td>223 (100)</td><td>162 (72.6)</td><td>< 0.0001</td></tr>
</table>
</td>
</tr>
</table>

Citation/EL	Method	Results
	of resting children (before immunisation) was measured using a pulse oximeter (Nelcor Puritan Bennet-3930 with Dura-Y infant sensor) attached to the finger or toe. Recordings were taken after stabilisation of the pulse oximetry reading for one minute. Age, weight, and current province of residence of the child were also recorded. For the ill child portion of the study, children were recruited at the time of presentation to the children's ward. The children were not selected for severity of illness or particular diagnostic groups, but represented all children admitted by two of the investigators over 12 month and four month periods. Diagnoses were assigned according to the presenting clinical features and the results of relevant investigations. Multiple diagnoses were recorded if present. Children were evaluated for the presence of ALRI: this included children with the WHO definitions of mild, moderate, severe, or very severe pneumonia, measles, and pertussis. They also included children with pulmonary tuberculosis in this group with ALRI. They recorded the presence or absence of the	<table><tr><td>Sick children, no ALRI</td><td>136</td><td>93 (86–96)</td><td>0</td><td>38 (27.9)</td><td>< 0.0001</td></tr><tr><td>Meningitis</td><td>40</td><td>86 (78–93)</td><td>3 (7.5%)</td><td>21 (53)</td><td>< 0.0001</td></tr><tr><td>Septicaemia</td><td>10</td><td>79 (57–94)</td><td>1 (10.0)</td><td>6 (60)</td><td>< 0.0001</td></tr></table> Table : ALRI, non-ALRI and diagnosis specific oxygen saturation in neonates <table><tr><td>Principal diagnosis</td><td>No.</td><td>Median (IQR) SpO_2</td><td>Number (%) with clinical ALRI</td><td>% with SpO_2< 88%</td><td>*P* value</td></tr><tr><td>Normal</td><td>67</td><td>94 (92–95)</td><td>0</td><td>1 (1.5)</td><td></td></tr><tr><td>Sick neonate</td><td>132</td><td>88 (66–94)</td><td>22 (16.7)</td><td>57 (43.2)</td><td>< 0.0001</td></tr><tr><td>ALRI</td><td>22</td><td>72 (52–85)</td><td>22 (100)</td><td>17 (77)</td><td>< 0.0001</td></tr><tr><td>Sick neonate, no ALRI</td><td>110</td><td>90 (72–96)</td><td>0</td><td>40 (36.4)</td><td>0.0002</td></tr><tr><td>Septicaemia</td><td>34</td><td>87 (59–93)</td><td>7 (20.6)</td><td>15 (44.1)</td><td>< 0.0001</td></tr></table> <u>Clinical signs predicting hypoxaemia</u> Table : Predictive value of clinical signs for hypoxaemia (SpO_2 < 88%) in the sick children (1 month to 5 years). <table><tr><td>Sign</td><td>Number with sign/number recorded</td><td>Sensitivity %</td><td>Specificity%</td><td>PPV%</td><td>NPV%</td><td>Relative risk</td></tr><tr><td>Not feeding</td><td>119/349</td><td>41.9</td><td>76.2</td><td>69.7</td><td>50.0</td><td>1.39</td></tr><tr><td>Cyanosis</td><td>78/356</td><td>37.9</td><td>98.1</td><td>96.2</td><td>55.8</td><td>2.18</td></tr><tr><td>Reduced activity</td><td>128/336</td><td>43.5</td><td>69.2</td><td>65.6</td><td>47.6</td><td>1.52</td></tr><tr><td>Respiratory rate > 60</td><td>180/359</td><td>67.0</td><td>71.1</td><td>74.4</td><td>63.1</td><td>2.01</td></tr></table>

Citation/EL	Method	Results
	following clinical symptoms or signs: inability to feed, reduced activity, cyanosis, fast respiratory rate, failure to resist examination, grunting, and head nodding. These signs were recorded before measuring the SpO_2, which was done with the child breathing room air, as described above. Age and weight of the child were also recorded.	

Failed to resist examination	100/346	29.0	44.3	56.0	44.3	1.00
Head nodding	27/356	10.7	96.2	77.8	46.5	1.45
Grunting	64/358	21.6	86.8	67.2	46.9	1.27

Table : Predictive value of clinical signs for hypoxaemia (SpO_2 < 88%) in the sick neonates.

Sign	Number with sign/number recorded	Sensitivity %	Specificity%	PPV%	NPV%	Relative risk
Not feeding	75/130	66.7	49.3	50.7	65.4	1.45
Cyanosis	49/132	71.9	89.3	83.7	80.7	4.34
Reduced activity	55/132	61.4	73.3	63.6	71.4	2.22
Respiratory rate > 60	41/132	33.3	70.7	46.3	58.2	1.10
Respiratory rate < 30	7/132	10.5	98.7	85.7	59.2	2.10
Filed to resist examination	35/126	42.6	83.3	65.7	65.9	1.93
Head nodding	2/132	3.5	100	100	57.6	2.36
Grunting	19/132	22.8	92.0	68.4	61.1	1.76

Table :Predictive models using minimal number of independently predictive variables for age and ALRI specific diagnoses

Predictive models	Odds ratio (95% CI)	Sensitivity %	Specificity %	PPV %	NPV %	Relative risk
Children 1–60 months with ALRI						

Citation/EL	Method	Results						
		Model 1 RR > 60 or Cyanosis or Not feeding	4.3 (2.2–8.7); *P*< 0.001	81.9	49.0	82.4	48.1	1.59
		Model 2 Respiratory rate > 60 or Cyanosis or Reduced activity	5.2 (2.6–10.4); *P*< 0.001	83.2	51.0	83.2	51.0	1.70
		Children 1–60 months, no ALRI						
		Model 1	6.7 (2.5–18.1); *P*< 0.001	82.8	58.2	46.8	88.5	4.07
		Model 2	2.1 (0.9–4.9); *P* = 0.09	71.4	45.6	36.7	78.3	1.69
		Neonates, all diagnostic categories						
		Model 1	3.9 (1.5–10.5); *P* = 0.007	89.1	32.3	50.5	79.3	2.44
		Model 2	5.0 (2.1–11.6); *P*< 0.001	83.6	49.3	55.4	80.0	2.77
		Model 3 RR < 30 or Cyanosis or Reduced activity	7.3 (3.3–16.4) ; *P*< 0.0001	78.2	67	64.2	80.3	3.26
		Model 4 Respiratory rate > 70, < 30 or	6.2 (2.6–14.5); *P*< 0.001	83.6	54.8	58.2	81.6	3.16

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Cyanosis or Reduced activity</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Model 5 Cyanosis or Reduced activity</td><td>8.0 (3.5–18.0)</td><td>78.2</td><td>69.0</td><td>66.2</td><td>80.3</td><td>3.36</td></tr>
</table>

Neonates with bradypnoea had a mean SpO_2 of 47% (SD 11.5%), while neonates with a respiratory rate greater than 60 had a mean SpO_2 of 74% (SD 3.8%) (P = 0.01).
</td></tr>
<tr><td>Gadomski[264]

<u>Study type:</u> Prospective cohort study
EL: II</td><td><u>Country:</u>
Egypt
<u>Aim:</u>
To evaluate the caretaker terms correlated with actual physical exam findings, pulse oximetry and radiographic diagnosis in children with ARI.
<u>Setting, inclusion/exclusion:</u>
The study sites were large OPD affiliated with major universities in Egypt between November 1990 to June 1991. children aged 2 months to 5 years presenting to the OPD were eligible if they had cough and were reported by caretaker or observed to have fast or difficult breathing. Infants < 12 months wheezing for the first time were eligible. Exclusion criteria included recurrent wheezing, duration of illness > 14 days, or underlying chronic</td><td>In all 688 children met the inclusion criteria, nine were excluded due to abnormal chest x-ray, leaving 679 participants. Pulse oximetry was performed on 651 children, chest-x-ray were available for 667 children and 635 children had both. The cut-off indicating oxygen desaturation was ≥ or < 90% oxygen saturation measured by pulse oximetry (SpO_2). Given the limited reliability of SpO_2< 70, readings of SpO_2< 70 were excluded (n = 7).

In all 446 (66%) children had elevated respiratory rate using age-specific WHO cut-offs. Of the 667 children with chest x-ray, 40% had radiographic pneumonia, 34% had normal chest x-ray and 7 had lower respiratory infection, 3% had bronchiolitis, 2% had hilar inflammatory change and 11% were indeterminate or unreadable.

Of the 651 children who had pulse oximetry, three quarters had oxygen saturation ≥93%, and 88% were ≥90%. Children with pneumonia had lowest mean SpO_2 of 92% compared with 97% in normal children.

Table : Caretaker recognition compared with pulse oximetry (%≥ or < 90%, n = 651)
<table>
<tr><th>Feature</th><th>Sensitivity %</th><th>Specificity %</th><th>PPV %</th><th>NPV %</th><th>Relative risk</th></tr>
<tr><td>Deep/fast breathing</td><td>89</td><td>35</td><td>18</td><td>95</td><td>3.6</td></tr>
<tr><td>Fast breathing</td><td>86</td><td>45</td><td>20</td><td>95</td><td>4.0</td></tr>
<tr><td>Chest move up and down</td><td>86</td><td>47</td><td>20</td><td>96</td><td>5.0</td></tr>
<tr><td>Wheeze</td><td>53</td><td>58</td><td>17</td><td>89</td><td>1.55</td></tr>
<tr><td>Coarse</td><td>68</td><td>56</td><td>20</td><td>92</td><td>2.5</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>illness such as asthma, cardiac, metabolic or neurological diseases. Children presenting with fever, with or without a runny nose, and no other respiratory signs were recruited as controls and underwent the same study.

The presence or absence of pneumonia was verified by chest x ray.

After informed consent, the caretaker was interviewed by the paediatrician to ascertain the length of illness, associated signs and symptoms, and the child's past medical history and immunisation.</td><td><table><tr><td>breathing sound</td><td></td><td></td><td></td><td></td><td></td></tr></table></td></tr>
<tr><td>Mower[265]

<u>Study type:</u>

Prospective cohort study.

EL: II</td><td><u>Country:</u>

US.

<u>Aim:</u>

To determine the utility of pulse oximetry as a routine fifth vital sign in acute paediatric assessment.

<u>Setting, inclusion/exclusion:</u>

This study was conducted from November 1993 to June 1994 at a university hospital ED. All patients younger than 18 years presenting to emergency triage were enrolled. Children were excluded from the study if they bypassed triage and were judged by the triage nurse or prehospital care</td><td>A total of 2602 children presented to the ED during the study period; 91 patients bypassed triage to undergo immediate resuscitation and evaluation. Triage nurses were unable to measure respiratory rates or SaO_2 accurately for 181 children (6.7%), and data questionnaires were lost for 3 patients. Triage pulse oximetry measurements and respiratory rates were obtained on the remaining 2327 individuals.

After the Northridge, CA, earthquake and surrounding hospital closures, they had an increase in patient visits and lacked sufficient personnel to inform physicians of the pulse oximetry results and collect data forms accurately. This forced them to exclude 80 children for whom pulse oximetry values had been measured but not communicated to physicians. An additional 120 children left our ED before completing their medical evaluations. The remaining 2127 patients form our study population. This population includes 934 girls (43.9%) and 1193 boys (56.1%). Ages ranged from birth to 17 years.

The physicians, after receiving triage pulse oximetry measurements at the time of patient disposition, ordered 12 additional diagnostic tests and 22 additional therapies in 29 (1.6%) of the 1822 children having triage pulse oximetry values of 95% or greater. Physicians ordered 81 additional diagnostic tests and 39 additional therapies in 95 (31%) of the 305 children having pulse oximetry readings of less than 95% (Chi ^{2} test; $P < 0.00001$). Physicians changed the admission plans for 5 of the 1822 patients with SaO_2 values of 95% or greater and for 5 of the 305 children with SaO_2 values of less than 95% (Chi $_2$ test; $P < 0$ .0061).

After receiving oximetry measurements, clinicians ordered additional pulse oximetry for 49 children and ordered an additional 31 tests (excluding pulse oximetry) for 23 children. Physicians ordered additional chest radiographs for 16 children, complete blood counts for 7, arterial blood gas analyses for 4, spirometry for 2, and ventilation-perfusion</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>personnel to be in need of immediate resuscitation or medical intervention. Children were also excluded if the triage nurse was unable to measure respiratory rate and pulse oximetry according to study protocols.

Triage nurses assessed each child and measured temperature, pulse, and blood pressure using pre-study triage techniques. Respiratory rates were measured by placing a stethoscope on the patient's chest wall and counting the auscultated breath sound for 1 minute. The nurses then assigned triage priorities based on the patient's condition and measurement of the four standard vital signs.

After the triage priority was determined, the nurses measured each patient's SaO_2 using a pulse oximeter (N-20; Nellcor Inc, Hayward, CA).

Pulse oximetry values were not recorded on the children's medical records but were withheld from physicians until they had completed a child's medical evaluation and were ready to discharge or admit each patient. Only the triage nurse knew the patient's triage oximetry value. Nurses temporarily linked children to their oximetry measurements</td><td>scanning for 2. The clinicians ordered antibiotics for an additional 15 children, supplemental oxygen for 11, and beta-agonists for eight. Five children initially scheduled for discharge were subsequently admitted.

Overall, for the 305 patients with SaO_2 values of less than 95%, the clinicians ordered 81 additional diagnostic tests for 62 patients (20%) and 39 additional treatments for 33 children (11%). Clinicians changed or added diagnoses for 25 children (8.2%).

Upper respiratory tract infection was initially diagnosed in 44 individuals, making it the most frequent diagnosis given to the 305 patients with SaO_2 measurements of less than 95%. An additional 6 diagnoses were made after the clinicians received the oximetry results. These 6 diagnoses represent 12% of the final 50 diagnoses of upper respiratory tract infection. Fourteen (28%) of these children underwent additional diagnostic testing after oximetry measurements were revealed, and 6 (12%) had adjustments made to their therapy. Asthma, pneumonia, congenital heart disease, and bronchitis were other diagnoses frequently seen in patients having oximetry values of less than 95%. No new cases of congenital heart disease were made on the basis of oximetry measurements, and pulse oximetry did not affect the treatment of these patients.

Table: Effect of Routine Pulse Oximetry on Diagnosis, Testing, and Treatment in 305 Children With Oxygen Saturation Values of Less Than 95%

<table>
<tr><th>Final Diagnosis*</th><th>No. of Patients Diagnosed Before Oximetry</th><th>Additional Patients Diagnosed After Oximetry (% Increase)</th><th>No. (%) of Patients With Changes in Testing</th><th>No. (%) of Patients With Changes in Treatment</th></tr>
<tr><td>URI/viral syndrome</td><td>44</td><td>6 (14)</td><td>14 (28)</td><td>6 (12)</td></tr>
<tr><td>Asthma/RAD</td><td>36</td><td>2 (5.6)</td><td>4 (11)</td><td>9 (24)</td></tr>
<tr><td>Pneumonia</td><td>23</td><td>3 (13)</td><td>16 (62)</td><td>11 (48)</td></tr>
<tr><td>Congenital heart disease</td><td>11</td><td>0 (0)</td><td>2 (18)</td><td>0 (0)</td></tr>
<tr><td>Bronchitis</td><td>5</td><td>1 (20)</td><td>3 (50)</td><td>2 (33)</td></tr>
<tr><td>Other</td><td>186</td><td>13 (7.0)</td><td>23 (12)</td><td>5 (2.7)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>by recording the unique identifying study number on a questionnaire attached to each chart. Physicians were asked to complete a brief questionnaire when they were ready to discharge or admit each child. Physicians were asked to specify whether chest radiography, complete blood count, spirometry, arterial blood gases, pulse oximetry, and ventilation-perfusion scanning had been used in evaluating each patient and whether antibiotics, β-agonists, supplemental oxygen, or hospital admission had been necessary. Physicians were also asked to supply their discharge diagnosis for each child.

Physicians were given the requested disposition forms along with the corresponding triage pulse oximetry value when the data questionnaire was complete. After receiving the triage pulse oximetry measurements, physicians were free to order any additional tests or therapies they thought indicated and were allowed to alter their dispositions and diagnoses.

To determine whether treatment was altered by the oximetry results, all diagnostic tests and therapies were abstracted from the ED medical record by an</td><td>* URI indicates upper respiratory tract infection; and RAD, reactive airway disease.

SaO_2 levels were related to the frequency with which physicians altered their medical treatment.

Physicians were most likely to change their treatment of patients with oximetry readings between 86% and 92%, with the greatest relative number of changes occurring at the 89% saturation level. Two-thirds of patients having SaO_2 values of 89% underwent additional testing, and 40% had changes made in their treatment. This level also had the highest rate of diagnostic changes, with 20% of the diagnoses changed as a result of pulse oximetry measurements.

Table : Changes in Treatment by Pulse Oximetry Value
<table>
<tr><th>Oxygen Saturation Level (%)</th><th>No. of Patients</th><th>Additional Changes in Testing (%)</th><th>Additional Changes in Treatment (%)</th><th>Additional Inpatient Admissions (%)</th><th>Changes in Diagnosis (%)</th></tr>
<tr><td>100</td><td>319</td><td>2 (0.6)</td><td>2 (0.6)</td><td>0 (0.0)</td><td>0 (0.0)</td></tr>
<tr><td>99</td><td>380</td><td>0 (0.0)</td><td>0 (0.0)</td><td>1 (0.3)</td><td>1 (0.3)</td></tr>
<tr><td>98</td><td>473</td><td>1 (0.2)</td><td>4 (0.8)</td><td>1 (0.2)</td><td>4 (0.8)</td></tr>
<tr><td>97</td><td>309</td><td>1 (0.3)</td><td>5 (1.6)</td><td>1 (0.3)</td><td>3 (1.0)</td></tr>
<tr><td>96</td><td>206</td><td>1 (0.5)</td><td>5 (2.4)</td><td>2 (1.0)</td><td>2 (1.0)</td></tr>
<tr><td>95</td><td>136</td><td>4 (2.9)</td><td>3 (2.2)</td><td>0 (0.0)</td><td>2 (1.5)</td></tr>
<tr><td>94</td><td>87</td><td>9 (10)</td><td>7 (8.0)</td><td>1 (1.1)</td><td>7 (8.0)</td></tr>
<tr><td>93</td><td>66</td><td>10 (15)</td><td>6 (9.1)</td><td>2 (3.0)</td><td>2 (3.0)</td></tr>
<tr><td>92</td><td>42</td><td>7 (16)</td><td>8 (19)</td><td>1 (2.4)</td><td>6 (14)</td></tr>
<tr><td>91</td><td>24</td><td>8 (33)</td><td>0 (0.0)</td><td>0 (0.0)</td><td>3 (12)</td></tr>
<tr><td>90</td><td>21</td><td>4 (19)</td><td>1 (4.8)</td><td>0 (0.0)</td><td>3 (14)</td></tr>
<tr><td>89</td><td>15</td><td>10 (67)</td><td>6 (40)</td><td>1 (6.7)</td><td>3 (20)</td></tr>
<tr><td>88</td><td>12</td><td>3 (25)</td><td>0 (0.0)</td><td>0 (0.0)</td><td>0 (0.0)</td></tr>
<tr><td>87</td><td>4</td><td>1 (25)</td><td>0 (0.0)</td><td>0 (0.0)</td><td>0 (0.0)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>investigator blinded to the pulse oximetry measurements. Tests and therapies were considered to have been ordered before oximetry disclosure if they were listed on the questionnaire.</td><td>
<table>
<tr><td>86</td><td>5</td><td>2 (40)</td><td>0 (0.0)</td><td>0 (0.0)</td><td>0 (0.0)</td></tr>
<tr><td>≤85</td><td>28</td><td>8 (29)</td><td>4 (14)</td><td>0 (0.0)</td><td>1 (3.6)</td></tr>
</table>
Seventy-three patients had SaO_2 values of 90% or less. Only 23 (32%) had tachypnoea (defined as a respiratory rate in the upper 5% by age), and only 35 (48%) had respiratory rates within the upper 20% for their age. Of this same group of 73 children, clinicians either rechecked pulse oximetry or admitted 50 (68%), whereas 23 children were discharged without having their pulse oximetry rechecked.
Of the 80 children who had pulse oximetry performed but not reported to physicians, 13 had SaO_2 values of 93% or less. Three were admitted to the hospital on their initial visit, and 1 had pulse oximetry measured as part of their medical evaluation. The remaining 9 patients were discharged by their treating physicians, who were unaware of the SaO_2 measurements. The department triage log enabled us to identify these patients and to obtain follow-up information on 8 of them. Six (75%) revisited the ED within 48 hours with the same conditions, and three (38%) were admitted at their revisits. Two patients reported uneventful recoveries without revisit. They were unable to obtain follow-up information on 1 child.
</td></tr>
</table>

Observation

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr>
<td>Kibirige[266]

Study type:

Retrospective data analysis with telephone survey to 1033 parents.

EL:3

Abbreviations: ICP, integrated care pathway; PAS, patient administration system</td>
<td>Country

UK

Aim:

To analyse retrospectively all referrals to the assessment unit during a seven year period, to determine their sources and destination.

Method, inclusion, exclusion:

The data have been collected over the past seven years since the unit first opened (between November 1994 and November 2001). Demographic information was collected and stored on a database within the unit. This has been cross checked using the hospital patient administration system (PAS), and a hand written register based in the unit. The demographic data and outcome of the consultation have been analysed retrospectively. Between August 2000 and December 2000 data were collected for each of the 1033 patients referred to the assessment unit. Parents of every child in this subgroup filled in a form as part of patient evaluation of the service. This information was followed by a telephone call to the parents within one week of attending the assessment unit. A further 300 randomly selected patients' notes were analysed to determine the investigations performed on those admitted for inpatient care and those discharged from the assessment unit.

The community nurses' service was</td>
<td>The number of children staying in hospital for less than 24 hours gradually increased, but there has been a decline over the past 2 years (figure was used to illustrate the findings). There is a similar trend for those staying in hospital for more than 24 hours, but the total numbers are significantly less than those staying less than 24 hours. These numbers include children who were admitted during the night when the assessment unit closes.

Historically, a referral equated to an admission before the unit was opened. Since the opening of the unit, 34.2% of the children referred to the unit have been assessed and sent home. The average period of stay in the assessment unit was 123 minutes for children who were sent home. (figure was used to illustrate the findings) Observation in the unit, waiting for medication from pharmacy, or waiting for results of investigations were the main contributors to the prolonged length of stay in the unit.

Table Sources of referrals
<table>
<tr><td>Source</td><td>Percentage</td></tr>
<tr><td>General practitioners</td><td>69</td></tr>
<tr><td>Accident and emergency</td><td>24</td></tr>
<tr><td>Self referrals</td><td>4</td></tr>
<tr><td>Others</td><td>3</td></tr>
</table>
Table : Frequency of medical problems
<table>
<tr><td></td><td colspan="2">Percentage</td></tr>
<tr><td>Diagnosis</td><td>n = 1033[a]</td><td>Armon et al n = 3802[b]</td></tr>
<tr><td>Respiratory</td><td>24.8</td><td>31</td></tr>
<tr><td>Gastrointestinal</td><td>20.4</td><td>22</td></tr>
<tr><td>Infection (not specified)</td><td>20.5</td><td>20</td></tr>
<tr><td>Severe multisystem</td><td>0.1</td><td></td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>analysed by looking at caseload referrals and type of care provided from January 1999 to December 2000. The number of extra hours worked by the community nurse has been used to estimate the ratio of community nurses required per patients referred per year.</td><td>
<table>
<tr><td>Central nervous system and epilepsy</td><td>6.1</td><td>5</td></tr>
<tr><td>Endocrine and diabetes</td><td>1.7</td><td></td></tr>
<tr><td>Accidental poisoning</td><td>2.1</td><td></td></tr>
<tr><td>Haematology and oncology</td><td>0.6</td><td></td></tr>
<tr><td>Genitourinary</td><td>1.3</td><td></td></tr>
<tr><td>Musculoskeletal</td><td>0.2</td><td></td></tr>
<tr><td>Dermatology</td><td>2.1</td><td>5</td></tr>
<tr><td>Cardiovascular</td><td>0.3</td><td></td></tr>
<tr><td>Allergy</td><td>0.8</td><td></td></tr>
<tr><td>Psychosocial</td><td>0.1</td><td></td></tr>
<tr><td>Feeding</td><td>1.2</td><td></td></tr>
<tr><td>Others</td><td>17.7</td><td>17</td></tr>
<tr><td colspan="3">[a]Children seen between August and December 2000.
[b]Accident and emergency over 1 year in Nottingham.</td></tr>
</table>
Of 1033 children, 682 were admitted. The majority of those would have been happy with home care if there had been sufficient support for them, but 45% were happier to be managed in hospital. At least 5% were unsure what would have been most appropriate.
Table :Parents’ views
<table>
<tr><td>Views</td><td>% response</td></tr>
<tr><td>Happy to be admitted</td><td>45.7</td></tr>
<tr><td>Happy to go home</td><td>48.1</td></tr>
<tr><td>Reluctant for admission</td><td>0.5</td></tr>
<tr><td>Admitted at parents’ request</td><td>0.4</td></tr>
<tr><td>Discharged against advice</td><td>0.2</td></tr>
</table>
</td></tr>
</table>

Citation/EL	Method	Results
		Not given | 5.1 Of those that were discharged from the assessment unit, 0.4% were seen in hospital again for the same problem within three days; another 15.9% spoke to either the family doctor or someone else—either a nurse in our unit or a non-medical person for reassurance. Of the 300 children whose notes were analysed for investigations performed, 150 had been admitted and 150 discharged from the assessment unit. The group admitted to the ward had 213 investigations performed, compared with 62 investigations in the group that was discharged. Urinalysis was the most common investigation in both groups, followed by a full blood count and tests for acute phase proteins. Thus children discharged from the assessment unit in this cohort did not have excessive tests performed on them. Figures were used to illustrate increasing workload referred to the community nurses. The quantifiable work was administration of intravenous antibiotics, but a considerable amount of reassurance and health education was also provided.

Diagnosis in secondary care

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td>Van Rossum[165]

<u>Study type:</u>
Systematic review
EL:1+</td><td>Aim:
To examine if Procalcitonin is a good early marker of infection in neonates and children.
Method:
Data for this review were identified by searching for articles on procalcitonin as a marker for bacterial infection in neonates, infants, and children in the PubMed database up to December 31, 2003. They searched only for papers in English. Review articles and comments on previously published articles were excluded. Search terms were ‘procalcitonin’ in combination with ‘neonatal’, ‘neonates’, ‘infants’, ‘children’, ‘pediatric’, and ‘paediatric’. 18, 45, 23, 53, 19, and seven articles, respectively, were</td><td>Neonatal infections:
Results of studies on the use of procalcitonin as an early marker of neonatal sepsis are contradictory. A significant increase in serum procalcitonin concentration during sepsis was found in both term neonates and a heterogeneous group of preterm neonates. This increase did not seem to be dependent on gestational age. These studies seem to show that procalcitonin is an early and specific marker of severe sepsis, by contrast with CRP. They confirm the importance of this marker in excluding infection shortly after birth.
However, six studies have concluded that procalcitonin is not a better early marker for neonatal sepsis than CRP. The lack of specificity was explained in part by significantly higher procalcitonin in non-infected infants with respiratory distress syndrome or haemodynamic failure than in non-infected infants who had neither of these conditions. Bonac and colleagues reported that neonates with either perinatal asphyxia, intracranial haemorrhage, pneumothorax, or after resuscitation had raised serum procalcitonin concentrations that did not differ from those of septic neonates up to 48 h after onset of clinical signs of distress or infection. Hypoxaemia, which is common to the different conditions of neonatal distress, could be responsible for increased procalcitonin concentrations. Prepartum and intrapartum administration of antibiotics may affect the concentration of procalcitonin in the umbilical cord, and postnatal administration of antibiotics will definitely influence postnatal procalcitonin concentrations. Prenatal, intranatal, and postnatal administration of antibiotics may therefore be a major confounder of the relation between procalcitonin and infection. In addition, lack of correction for reference ranges for neonatal procalcitonin values may also have influenced the outcome of procalcitonin as a marker for bacterial infection.
That results are contradictory is not surprising given the highly diverse groups of ill neonates with a mixture of diagnoses and conditions. Variations in study design, definition of infection, cut-off points of procalcitonin and CRP, and wide-ranging differences in postnatal age (hours to weeks) lead to difficulties in comparing studies. Procalcitonin may be a valuable marker for the detection of early neonatal infection when reference values, the clinical condition, and the administration of antibiotics are taken into account in both term and preterm neonates. Chiesa and colleagues 18 studied all perinatal events and concluded that, compared with the increases in procalcitonin caused by these perinatal events, the magnitude of procalcitonin response to infection is much greater. Both the specificity and sensitivity of procalcitonin were greater than those obtained for CRP.

Table : Neonatal infections
<table>
<tr><th rowspan="2">Study, year</th><th rowspan="2">Population</th><th rowspan="2">Number in study</th><th rowspan="2">Age</th><th rowspan="2">Gold standard</th><th colspan="2">Cut-off</th><th colspan="2">Sensitivity (%)</th><th colspan="2">Specificity (%)</th><th colspan="2">PPV (%)</th><th>NPV (%</th></tr>
<tr><th>CRP (mg/L)</th><th>PCT (ng/mL)</th><th>CRP</th><th>PCT</th><th>CRP</th><th>PCT</th><th>CRP</th><th>PCT</th><th>CRP</th></tr>
<tr><td>Resch et al,2003</td><td>Preterm and full-term suspected of infection</td><td>76</td><td>< 12 h</td><td>Clinical signs of sepsis or increased risk for infection</td><td>2·5</td><td>2</td><td>69</td><td>83</td><td>96</td><td>61</td><td>96</td><td>76</td><td>67</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>8</td><td>6</td><td>49</td><td>77</td><td>100</td><td>91</td><td>100</td><td>93</td><td>58</td></tr>
</table>
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Citation/EL	Method	Results													
	available. Of these 165 articles, 74 were duplicates. After also excluding articles not written in English (n = 17), review articles (n = 9), case reports (n = 1), and comments on previously published articles (n = 6), the abstracts of the remaining 58 articles were read to determine whether the subject of the article was 'procalcitonin as early marker for bacterial infection in neonates or children'. 12 articles were excluded after reading, because the subject was not procalcitonin as an early marker for bacterial infection in neonates or children. Bibliographies of all included articles were checked for additional publications and did not reveal more articles. 46 original articles were available for this														
							14	..	63	..	100	..	92	..	64
		Engle et al,2003	Term neonates, respiratory symptoms > 6 h postnatal	51	8–12 h and 48 h postnatal	Radiographic findings of pneumonia	1	1	..	..	..	..	..	..	..	..
		Kordek et al, 2003	Preterm and full-term infected and non-infected	187	Umbilical cord	Clinical signs ± positive sepsis screen	2·5	1·2	22	69	97	81	20	42	86	93
		Koskenvuo et al, 2003	Critically ill neonates	65	< 12 h 72 h postnatal	Blood culture or clinical signs and positive sepsis screen	..	..	..	..	..	..	..	..	..	..
		Chiesa et al, 2003	Critically ill, preterm; infected and non-infected	219	Umbilical cord 24 h 48 h	Blood culture SNAP-PE37	0 h: 4	0 h: 1	74	79	83	95	..	..	..	..
							24 h:10	24 h: 100	89	95	87	96				
							48 h:10	48 h: 50	89	84	84	100				
		Blommendahl et al,2002	Preterm and full-term suspected of infection	169	Unknown	Blood culture	30	1	58	77	84	62	24	16	94	97
		Guibourdenche et al,2002	Preterm and full-term infected and non-infected	136	At birth	Blood/CSF culture ± clinical signs of sepsis ↑ or ↓ WBC	7·5	2·5	68	87	80	90	81	86	72	93
		Athhan et al, 2002	Full-term infected vs. full-term	34	Unknown	Tollner's scoring system	..	..	..	..	..	..	..	..	..	..

Citation/EL	Method	Results														
	review.		controls													
		Janota et al,2001	Preterm infants (< 1500 g and < 31 weeks)	37	Umbilical cord +1 h, 48–72 h, and day 7 post natal	Blood culture or clinical signs and positive sepsis screen	1	2	25	75	90	75	..	..	..	..
		Enguix et al,, 2001	Critically ill, term neonates; control group	20	3–30 days	Clinical + laboratory criteria	23	6·1	96	99	84	89	80	90	97	99
				26	3–30 days											
		Sikora et al,2001	Preterm and full-term suspected of infection; control group	13	< 12 h, 12–24 h after termination of antibiotic therapy	Blood culture or clinical signs and positive sepsis screen	..	..	..	..	..	..	..	..	..	..
				20												
		Bonac et al,2000	Critically ill, preterm, and term neonates; control group	58	0–20 days	Blood culture or clinical signs and positive sepsis screen	0 h: 14	0 h: 10	36	59	92	82	43	36	89	92
							24 h: 29	24 h: 13	44	50	100	100	100	100	91	92
				25			48 h: 12	48 h: 3	68	52	83	91	42	50	94	92
		Franz et al,1999	Critically ill, preterm, and term neonates	162	0–11 days	Blood culture or clinical signs and positive sepsis screen	0 h: 10	0 h: 0·27	28	80	97	53	81	41	77	87
								12–36 h:	..	57	..	66	..	40	..	79

Citation/EL	Method	Results

						0·5								
						36–60 h: 3·5	..	30	..	91	..	56	..	77
Lapillonne et al. 1998	Critically ill, preterm and term neonates	150	0–10 days	Blood culture or clinical signs	..	5	..	84	..	50	..	..	..	..
Chiesa et al, 1998	Critically ill	126	0–48 h and 3–30 days	Blood culture or clinical signs and positive sepsis screen	1	0·6	46	86	..	..	..	..	..	..
								70	100	..	100			
Monneret et al, 1997	Critically ill, preterm, and term neonates; control group	39	0–28 days	Blood/CSF/urine culture or two peripheral cultures with clinical signs of sepsis	..	..	..	..	..	..	..	..	..	..
		49												
Gendrel et al, 1996	Critically ill, preterm, and term neonates; control group	68	0–15 days	Blood culture or clinical signs and positive sepsis screen	10	..	..	..	..	..	..	..	..	..
		86												

AUC ROC = area under the curve, receiver operating characteristic; CRP = C-reactive protein; CSF = cerebrospinal fluid; NPV = negative pre
PCT = procalcitonin; PPV = positive predictive value; SNAP-PE = score for neonatal acute physiology—perinatal extension; WBC = white blood cell count; .. =

Sepsis and meningitis:

Citation/EL	Method	Results

All studies on procalcitonin in children with sepsis, septic shock, or meningitis report that procalcitonin is an excellent marker of severe bacterial infection and that it has a diagnostic performance significantly greater than that of CRP concentration and leukocyte count. Sensitivity and specificity of procalcitonin varied from 83% to 100% and from 70% to 100%, respectively. For CRP, sensitivity and specificity were in a lower range (73–88% and 50–89%, respectively). The diagnostic value of procalcitonin was excellent, both for discriminating between viral and bacterial infections and between invasive and localised bacterial infections. Cut-off values differ widely between the studies, which can be a major practical problem when procalcitonin values are used in clinical practice. Most of the studies reported a cut-off value of 2 ng/mL as the best value for distinguishing between invasive and localised bacterial infections and between viral and bacterial infections.

Gendrel and colleagues found procalcitonin to be a better marker than CRP for distinguishing between bacterial and viral infections in children in the emergency room. They also found this for children who developed fever up to 12 h before presentation in the hospital. All patients with sepsis and meningitis had procalcitonin concentrations higher than the cut-off value of 0·6 ng/mL in the first analysis in the emergency department. In addition, the rapid semiquantitative test offered a better diagnostic performance than CRP, particularly in detecting invasive bacterial infections and in differentiating them from localised bacterial or viral infections. However, for the follow-up of procalcitonin concentrations and routine daily measurements, the quantitative luminometric assay is preferable.

Procalcitonin is also a useful indicator of the severity of bacterial infections. Three studies reported persistently increased procalcitonin concentrations associated with multiple organ failure and mortality in children with bacterial sepsis. However, Hatherill and colleagues reported that a single procalcitonin measurement is an inadequate tool for prognosis and that serial procalcitonin measurements might be of more value in the monitoring of the response to treatment in septic shock.

Procalcitonin is an excellent marker for severe, invasive bacterial infection in children. However, this test cannot be presented as the gold standard. The negative predictive value is not always 100%, and therefore a low procalcitonin value can falsely reassure physicians. However, it performs better than tests currently used (white blood cell count [WBC], CRP), and maybe a useful adjunct in diagnosis.

Table : Sepsis and meningitis

Study, year	Population	Number in study	Age	Aim	Gold standard	Cut-off		Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)		Relative Risk	
						CRP (mg/L)	PCT (ng/mL)	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT
Fernandez Lopez et al, 2003	Fever requiring hospital admission	445	0·08–3	1	Positive culture in blood/CSF	27·5	0·59	78	91	75	94	69	91	81	90	7.67	9.1
Casado-Flores et al,	Admission to PICU due to	80	0·08–16	2	Clinical+ laboratory	..	..	..	..	..	..	..	..	..	..	..	..

Citation/EL	Method	Results																	
		2003	sepsis				criteria												
		Han et al, 2003	Sepsis or septic shock; critically ill controls without sepsis	78	4·8	1, 2	Clinical+ laboratory criteria (sepsis, septic shock)	..	..	..	..	..	..	..	..	..	..	..	..
				12	5														
		Prat et al,2003	Fever < 12 h; bacterial sepsis/meningitis; aseptic meningitis; localised bacterial infection; controls	25	0·08–12	1	Positive culture in blood/CSF	40	2	88	100	50	100	64	100	91	100		
				18															
				22															
				25															
		Carrol et al, 2002	Fever+purpuric rash	108	0·07–15·9	3	Positive blood culture	30	2	81	94	89	93	91	95	76	91	3.79	10.56
		Van der Kaay et al, 2002	Meningococcal sepsis±septic shock	64	0·77–12·4	3	Severity, survivors vs. non-survivors	..	..	..	..	..	..	..	..	..	..	..	..
		Enguix et al, 2001	Critically ill; controls	52	2–12	2	Clinical+ laboratory criteria	22	8	89	100	81	100	80	100	89	100	8.89	--
				64															
		Hatherill et al, 2000	Septic shock	75	0–16	3	Clinical+ laboratory criteria	..	..	..	..	..	..	..	..	..	..	..	..
		Somech et al, 2000	Unexplained fever/sepsis	38	0·3–11	3	None	..	..	..	..	..	..	..	..	..	..	..	..

Citation/EL	Method	Results

	examination																
Hatherill et al, 1999	Admission to PICU	175	0·1–16·1	1	Positive bacteria isolate	50†	20†	76†	83†	80†	92†	76†	90†	80†	87†	3.80	6.92
						..	2‡	..	100‡	..	70‡	..	78‡	..	100 ‡	--	--
Gendrel et al,1999	Hospital admission for fever > 38·5 °C, known pathogen	360	0·3–15	1	Positive bacterial or viral isolate	§ 40§	1§	73§	83§	88§	93§	76§	86§	86§	91§	5.43	9.56
Gendrel et al, 1997	Hospital admission for meningitis	59	0·4–13	1	Positive bacterial or viral CSF culture	..	5	..	94	..	100	..	..	..	..	..	..
Assicot et al, 1993	Hospital admission for severe infection	79	0–10	1	Positive bacterial or viral isolate	..	..	..	..	..	..	..	..	..	..	..	..

* The aim of the study was to: 1 = use procalcitonin (PCT) as a diagnostic marker of severe bacterial infection; 2 = use procalcitonin as a prognostic marker of sepsis/multiple organ failure.; 3 = determine correlation between C-reactive protein (CRP) and PCT.
† All values for septic shock only;
‡ All values for children with septic shock and/or bacterial meningitis;
§ To distinguish between invasive or localised bacterial infections and viral infections;
¶ To distinguish between invasive bacterial infections and localised bacterial or viral infections. AUC ROC = area under the curve, receiver operating characteristic; CSF = cerebrospinal fluid; NPV = negative predictive value; PPV = positive predictive value; PICU = paediatric intensive care

Lower respiratory tract infection:

Bacterial pneumonia cannot be differentiated from viral pneumonia on the basis of a patient's characteristics, routine laboratory tests, or chest radiographic findings. WBC or serum CRP concentration sometimes helps to differentiate between bacterial or viral causes. However, results of studies on the use of these markers have been inconsistent. Early indicators of cause and severity would help with the decision of whether to prescribe or to withhold antibiotics.

Citation/EL	Method	Results

Only one study has been done among infants with bronchiolitis on procalcitonin and CRP values during the respiratory syncytial virus season. This study showed that serum procalcitonin values were less than 0·5 ng/mL in 96% of the children with respiratory syncytial virus bronchiolitis without bacterial superinfection and that serum CRP values were less than 8 mg/L in 69% of these children. Six studies have been published on the use of procalcitonin as a marker of bacterial causes of lower respiratory infection. Results of these studies are inconsistent. Three studies concluded that procalcitonin differentiates between bacterial infections and viral infections more effectively than CRP, WBC, or interleukin −6 in emergency department situations. However, another three studies stated that measurement of serum procalcitonin is of little value in differentiating between bacterial and viral pneumonia in children.

Table : Respiratory tract infections

Study, year	Population	Number in study	Age	Aim	Gold standard	Cut-off		Sensitivity (%)		Specificity (%)		PPV (%)		N
						CRP (mg/L)	PCT (ng/mL)	CRP	PCT	CRP	PCT	CRP	PCT	C
Korppi et al, 2003	Radiologically confirmed CAP	190	0–15	1	Chest radiograph, positive bacterial/atypical/viral isolates	60	0·5	..	46	..	52	--·	65	.
Resch et al, 2003	Infants admitted to hospital with bronchiolitis	48	0·04–1	2	Rapid RSV test on nasopharyngeal aspirate; bacterial blood culture	..	..	..	..	..	..	..	..	.
Prat et al,2003	ER clinical signs of lower RTI	85	0·5–10	3	Blood cultures, nasopharyngeal aspirate for viral studies	65	2	79	69	67	79	..	..	.
				4				90	90	60	74			
Hatzistilianou et al,2002	Hospital admission for clinical signs of lower RTI	73	2–14	4	Chest radiograph, positive bacterial/atypical/viral isolates	2	2	96	100	38	98	42	93	.
Korppi et	Hospital	58	3	5	Chest radiograph,	..	0·5	..	55	..	71	..	..	.

Citation/EL	Method	Results

al,2001	admission for clinical signs of lower RTI		(mean)		positive bacterial/atypical/viral isolates										
							1		32		88				
							2		8		95				
Moulin et al, 2001	Hospital admission for clinical signs of lower RTI	72	0·2–13	4	Positive bacterial/atypical/viral isolates, seroconversion	20	0·5	88	95	40	80	72	80	67	88
						60	1	70	86	52	90	81	90	58	80
							2	··	63	··	96	··	96	··	60
Toikka et al,http://www.sciencedirect.com/- bib69 2000	Hospital admission for clinical signs of lower RTI	126	0·1–17	3, 5	Positive bacterial/atypical/viral isolates, seroconversion	80	2	59	50	68	80	··	··	··	··
						150	7	31	19	88	98	··	··	··	··

* To use procalcitonin (PCT) to differentiate between: 1 = viral and bacterial causes of community acquired pneumonia (CAP) in the primary healthcare setti bacterial causes of bronchiolitis; 3 = viral and bacterial or atypical causes of CAP; 4 = viral or atypical and bacterial causes of CAP; 5 = viral and bacterial or CAP. AUC ROC = area under the curve, receiver operating characteristic; CRP = C-reactive protein; ER = emergency room; NPV = negative predictive value predictive value; RSV = respiratory syncytial virus; RTI = respiratory tract infection; ·· = not available.

When assessing the usefulness of procalcitonin a few pitfalls have to be taken into account. First, results depend on the accuracy of the aetiological diagnosis of lower respiratory tract infection. Diagnosis of pneumococcal infection was based mainly on immune complex assays in paired sera or antigen assays in urine. These tests have thus far been used only for research purposes in specialised laboratories, and their clinical value has not been established. Prat and colleagues analysed differences between pneumococcal pneumonia diagnosed by blood cultures and by urinary antigen and found no differences in WBC, CRP, or procalcitonin. This suggests that a pneumococcal pneumonia diagnosed by urinary antigen is as reliable as pneumococcal pneumonia diagnosed by blood culture. In some children, pneumococcal infection was diagnosed only by immune complexes. These children may have had another localised infection with Streptococcus pneumoniae-for example, otitis media-without true bacterial pneumonia. Second, the use of antibiotics before enrolment to the study or before the measurement of procalcitonin could be a major confounding factor. Procalcitonin concentration decreases rapidly if the bacterial infection is treated, reaching normal values within 1 or 2 days, whereas CRP

Citation/EL	Method	Results
		concentrations can increase during the first few days of antibiotic treatment. Toikka and colleagues found a marked overlap of procalcitonin and CRP within bacterial and viral causes. They hypothesised that some bacterial pneumonias are mild with only minor changes on the chest radiograph and with a modest host inflammatory response, and that some of the viral pneumonias are severe with major changes on the chest radiograph and in the host response. It is currently not possible to determine whether a patient should be given antibiotics solely on the basis of procalcitonin concentration, but high values indicate the presence of bacterial infection. Further studies with an adequate definition of bacterial lower respiratory infection, and without pre-treatment with antibiotics, should be done. UTI: The diagnosis of UTI is often not straightforward in paediatric practice. Infection of the lower tract is more likely to spread to the upper tract and kidneys in children than in adults. The non-specific nature of signs and symptoms in febrile infants and children makes the clinical differentiation between acute pyelonephritis and lower UTI difficult. Acute pyelonephritis should be distinguished from lower UTI because it can lead to chronic renal damage and, in the event of extensive renal scarring, can lead to arterial hypertension and renal insufficiency. 99mTc-dimercaptosuccinic acid (DMSA) is an isotope–labelled substrate that is absorbed in the proximal tubules. Its renal uptake can be measured and affected areas are seen as uptake defects. This test is considered the gold standard for the diagnosis of acute pyelonephritis when done in the acute phase and for the diagnosis of renal scarring secondary to pyelonephritis 5–6 months after the infection episode. However, DMSA scintigraphy is an expensive investigation that is not readily accessible in all centres. It also exposes the patient to radiation, and does not differentiate between old scarring and acute parenchymal involvement unless a follow-up scan is done. Procalcitonin and CRP were assessed as tests that could possibly distinguish lower UTI from acute pyelonephritis at the time of diagnosis. Benador and colleagues noted a 100% sensitivity of CRP. Thus, all children with normal CRP values could be safely considered not to have acute pyelonephritis and would not require either DMSA scans or early parenteral antibiotic therapy. However, the low specificity (26·1%) limits its clinical usefulness and leads to unnecessary hospital admissions. The specificity of procalcitonin (82·6%) was found to be much higher than that of CRP. The sensitivity of an increase in procalcitonin was 70·3%, and 11 children were found with very mild (defect covering < 5% surface area) or mild lesions (defect covering 5–10% surface area) with a normal procalcitonin value. Thus, procalcitonin alone cannot be used to identify all renal lesions because 30% of patients had normal procalcitonin concentrations despite grade 1 and 2 lesions. However, procalcitonin is found to correlate with the severity of renal lesions at time of diagnosis, and possibly with the risk of permanent scarring. Prat and colleagues reported a significant correlation between high procalcitonin values at the time of admission and renal damage. In addition, they found that procalcitonin yields a high negative predictive value of renal damage, meaning that a low procalcitonin value at the time of admission, despite clinical signs of pyelonephritis, points to a low risk of renal scarring. These results are in accordance with the other three studies that were done. Gervaix and colleagues examined the correlation between the quantitative and the rapid semiquantitative test. The blood samples tested with both methods showed a good correlation. No result above 0·5 ng/mL with the quantitative method was below the threshold of detection (0·5 ng/mL) of the rapid test. In conclusion, the data indicate that the procalcitonin test on admission has a high sensitivity and specificity for differentiating between acute pyelonephritis and lower UTI in infants and children, when compared with the low specificity of CRP or WBC. Procalcitonin measurement might therefore be a useful and practical tool for the diagnosis of acute pyelonephritis in infants and children, and allow informed decisions to be made about parenteral or oral antibiotic treatment in these patients. The use of the rapid semiquantitative test needs further evaluation.

Citation/EL	Method	Results

Table : UTI

Study, year	Population	Number in study	Age	Aim	Gold standard	Cut-off		Sensitivity (%)		Specificity (%)		PPV (%)		NP
						CRP (mg/L)	PCT (ng/mL)	CRP	PCT	CRP	PCT	CRP	PCT	CR
Prat et al,2003	ER clinical signs of UTI and abnormal urinalysis	77	0·1–12	1	Positive urine culture; DMSA scan for renal scarring	20	1	62	92	34	92	23	32	95
Smolkin et al, 2002	ER clinical signs of UTI and abnormal urinalysis	64	0–3	2	Positive urine culture; DMSA scan for renal involvement	20	0·5	100	94	19	90	31	86	10(
Gervaix et al, 2001	ER clinical signs of UTI and abnormal urinalysis	54	0–16	2, 3	Positive urine culture; DMSA scan for renal involvement	40	0·5†	68	74	55	85	··	··	··
Benador et al, 1998	ER clinical signs of UTI and abnormal urinalysis	80	0·1–16	1, 2	Positive urine culture; DMSA scan for renal involvement	10	0·6	100	70	26	83	··	··	··

* Aim of study was to: 1 = use procalcitonin (PCT) as a discriminator between uncomplicated urinary tract infection (UTI) and severe acute pyelonep
2 = use PCT as a discriminator between uncomplicated UTI and severe acute pyelonephritis; 3 = determine the correlation between the quantitative
Diagnostica) and the rapid semi-quantitative PCT test (Brahms PCT-Q, Brah
† Brahms PCT-Q test was used. AUC ROC = area under the curve, receiver operating characteristic; CRP = C-reactive protein; DMSA = 99mTc
ER = emergency room; NPV = negative predictive value; PPV = positive predictive value;·· = not available.

Fever without localizing signs:

Citation/EL	Method	Results

Fever without localising signs in young children is a difficult diagnostic problem, since clinical signs and symptoms are often unreliable predictors of a serious bacterial infection. Although most of these children have benign, self-limiting diseases, a few are at risk of developing a severe bacterial infection, which requires administration of parenteral antibiotics. Galetto-Lacour and colleagues reported the results of procalcitonin used in children with fever without localising signs. Children treated with antibiotics during the preceding 2 days were excluded. Procalcitonin and CRP resulted in a similar sensitivity and specificity for predicting serious bacterial infection (bacteraemia, pyelonephritis, lobar pneumonia, and meningitis). A severe bacterial infection was diagnosed in 23% of the children (n = 28: four bacteraemia, 19 pyelonephritis, five lobar pneumonia). A higher sensitivity and specificity for procalcitonin than for CRP has previously been reported by the same group in children with pyelonephritis. http://www.sciencedirect.com/- bib80 Given the high number of children with pyelonephritis in this group of children with fever without localising signs, it is surprising that this study results in equal sensitivity and specificity for CRP and procalcitonin. The diagnosis of pneumonia was based on chest radiography, which has been shown not to be discriminative between viral and bacterial causes. Therefore, these children could have had a viral pneumonia, which might result in a lower specificity of procalcitonin in this study. Galetto-Lacour and colleagueshttp://www.sciencedirect.com/-bib83 reported a similar study which used the rapid semiquantitative test. This study, in which 29% of the children were diagnosed with a severe bacterial infection (n = 29: four bacteraemia, 21 pyelonephritis, two lobar pneumonia, one mastoiditis, one retropharyngeal abscess), showed the same results as their previous study. Further studies with an adequate definition of severe bacterial infection are needed to determine the value of procalcitonin as a marker for fever without localising signs in children.

Table 5 : Fever without localizing signs:

Study, year	Population	Number in study	Age	Aim	Gold standard			Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)		Relative Risk	
						CRP (mg/L)	PCT (ng/mL)	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT	CRP	PCT
Galetto-Lacour et al, 2003	Fever > 38 °C and no localising signs of infection	99	0·02–3	CRP/PCT culture as a discriminator for severe bacterial infections	Blood/CSF/, urinary culture + DMSA defects; chest radiograph	40	0·5	79	93	79	74	90	96	61	61	2.31	2.46
Galetto-Lacour et al, 2001	Fever > 38 °C and no localising signs of infection	124	0·02–3	CRP/PCT as a discriminator for severe bacterial infections	Blood/CSF/culture, urinary culture+DMSA defects; chest radiograph	40	0·9	89	93	75	78	96	97	51	55	1.96	2.16

AUC ROC = area under the curve, receiver operating characteristic; CRP = C-reactive protein; CSF = cerebrospinal fluid; DMSA = 99mTc-

Citation/EL	Method	Results

dimercaptosuccinic acid; ER = emergency room; NPV = negative predictive value; PCT = procalcitonin; PPV = positive predictive value;·· = not available.

Fever in paediatric oncology

In neutropenic cancer patients, early markers are needed that are regulated or released independently of the leukocyte count and of the activity of the underlying disease. Studies in adults have shown that immunocompromised patients are capable of producing high serum concentrations of procalcitonin during severe systemic bacterial or fungal infections. Fleischhack and colleagues showed that the activity of the underlying malignant disease, the chemotherapy-induced tissue damage, and the severity of neutropenia did not cause substantial increases in plasma concentrations of procalcitonin. In another study, they concluded that the overall diagnostic efficiency of procalcitonin was superior to that of CRP in the early detection of Gram-negative bacteraemia in fever without localising signs. However, both sensitivity and specificity are low compared with other studies on the use of procalcitonin in children with sepsis. Sauer and colleagues reported that serum procalcitonin correlates with the severity of sepsis in paediatric recipients of bone-marrow transplants who are profoundly immunocompromised, and that it may reliably identify children with a high mortality risk. The use of procalcitonin in febrile neutropenic children has to be established in future studies, but with a high specificity for Gram-negative bacteraemia (97–99%) a low procalcitonin concentration is reassuring for the physician.

Table : Fever in paediatric oncology

Study, year	Population	Number in study	Age	Aim	Gold standard	Cut-off		Sensitivity (%)		Specificity (%)		PPV (%)	
						CRP (mg/L)	PCT (ng/mL)	CRP	PCT	CRP	PCT	CRP	PCT
Sauer et al 2003	Bone-marrow-transplant recipients	47	1–27	1, 2, 3	ACCP-SCCM definition	50	1	100	56	41	87	46	69
Barnes et al, 2002	Febrile neutropenia	··	··	4	Duration of admission > 5 days	··	0·2	··	80	··	35	0	··
Fleischhack et al,2000	Febrile neutropenia	51	0·7–31·8	5, 6	Positive culture of urine, faeces, throat swabs, bronchoalveolar	10	0·3	100	80	21	44	··	··
						50	0·5	22	60	73	85	··	··
						100	1·0	25	50	95	97	··	··
							5·0	··	40	··	99	··	··

Citation/EL	Method	Results

	Control group	35	1·2–28·8		lavage± clinical signs	10	0·3	14	64	81	69	..	..	..	..
						50	0·5	76	95	39	35	..	..	..	..
						100	1·0	96	100	10	15	..	..	..	..
							5·0	..	100	..	9	..	..	..	..
de Bont et al,2000	Febrile neutropenia	49	..	6	ACCP-SCCM definition	..	0·5	94	28	40	79	38	33	95	7

* Aim of study was: 1 = to compare serum levels of procalcitonin (PCT) and C-reactive protein (CRP) during sepsis; 2 = to determine predictive value of PCT fo sepsis; 3 = to determine correlation between PCT and severity of sepsis; 4 = to determine predictive value of PCT on length of admission; 5 = to use PC response to antibiotic therapy; 6 = to determine predictive value of PCT for severe systemic infection. ACCP-SCCM = American College of Chest Physicians–S Care Medicine; AUC ROC = area under the curve, receiver operating characteristic; NPV = negative predictive value; PPV = positive predictive value; .. = not av

Citation/EL	Method	Results

Thayyil[167]

Study type: prospective cohort study

EL: II

Country:

UK

Aim:

To compare diagnostic accuracy of procalcitonin for early diagnosis of serious bacterial infection (SBI) in children presenting with fever and no focus of infection.

Setting, inclusion/ exclusion:

They prospectively enrolled children (1-36 mo) presenting to the paediatric units of two university hospitals with fever without localising signs (FWSL) between January 2003- September 2003. All children had blood cultures,

The study included 86 children and 14 were exclude with a total of 72 children. Mean age was 18.5 months (ranged 1-36 months) and median duration of febrile illness was 2 days (1-8 days). Eight of them (11%) and SBI.

Table : Diagnostic utility of PCT (quantitative test) compared with CRP, WBC and YOS in diagnosis of SBI.

	Sensitivity %	Specificity %	PPV	NPV	Relative Risk
CRP> 50 mg/l	75	68.7	23	95.6	5.23
PCT> 0.5 ng/l	87.5	50	17.9	96.9	5.77
PCT> 2ng/l	50	85.9	30.7	93.2	10.96
WBC>15x10^5/l	50	53.1	11.8	89.5	1.12
Combination*	50	95.3	57	93.8	9.19
YOS	87.5	67.2	25.9	97.7	11.3

*: PCT> 2ng/l+ CRP> 50 mg/l+ WBC>15x10^5/l, and negative combination test is any of these negative.

Citation/EL	Method	Results
	urine cultures, white blood cell counts (WBC), chest X-ray, C-reactive protein (CRP) and procalcitonin (PCT) and YOS done at presentation. They excluded children who had taken antibiotics in the past 72 hours immune deficient children and children who had fever for more than 7 days.	
Galetto-Lacour[178] Study type: prospective cohort study EL: II	Country: Switzerland Aim: To compare the value of different rapid tests and the WBC count for predicting SBIs in children with fever without source (FWS). Setting, inclusion/ exclusion: In the ED of the University Children's Hospital of Geneva, they included 110 children 7 days to 36 months. Eleven children were excluded (4 were older than 3 years, 2 received antibiotics, 1 had a temperature <38 °C, 2 had focal symptoms already at the inclusion, and 2 had insufficient blood samples), so the data of 99 children were analyzed. Fever was defined as rectal temperature ≥38 °C. Children	All children had a WBC count with differential and a determination of CRP, PCT, and IL-6 values. Toxic-appearing children had a full sepsis workup, were admitted to the hospital, and were given parenteral antibiotics. Nontoxic-appearing children, from 1 week to 90 days of age or from 91 days to 36 months of age with fever ≥39 °C, had a urine collection by suprapubic aspiration, transurethral bladder catheterization, or midstream catch for analysis and culture. Blood was systematically cultured in children with leukocytes >15 g/L or band counts >1.5 g/L. In children from 91 days to 36 months of age with fever ≥38 °C but <39 °C, urine and blood culture were not performed unless biological risk factors (leukocytes >15 g/L, band counts >1.5 g/L, or leukocyturia) were present. A spinal tap was performed when meningitis was suspected. Erythrocyte, platelet, and WBC counts were performed in blood samples mixed with ethylenediaminetetraacetic acid (EDTA) using an automated cell counter. Band form was counted manually by trained technicians. CRP value was determined in 50 µL of EDTA-blood with a rapid (15 minutes) immunometric method (Nycocard CRP) according to the instructions of the manufacturer. Procalcitonin was measured by a rapid semiquantitative immunochromatographic test (Brahms PCT-Q; Brahms Diagnostica, Berlin, Germany) in 20 minutes (range of results: <0.5 ng/mL, ≥0.5 ng/mL, ≥2 ng/mL, and ≥10 ng/mL). Briefly, 200 µL of plasma-EDTA was applied onto the test strip. PCT in the sample is bound by mouse anti-calcitonin antibodies conjugated with colloidal gold to form a complex. This complex moves by means of capillarity through an area containing fixed anti-calcitonin antibodies to form a sandwich complex that can be seen as a reddish band. The colour intensity of the band is directly proportional to the PCT concentration of the sample. IL-6 was measured using a lateral flow semiquantitative immunoassay in 20 minutes. Briefly, 100 µL of plasma-EDTA was pipetted onto the test strip. IL-6 present in the sample binds to a monoclonal anti–IL-6 antibody conjugated to gold particles, flows through the test system, and finally overflows a test band coated with a second monoclonal antibody specific for IL-6. The accumulated gold particles are immobilized on the test band and become visible as a red-blue band. Colour intensity is directly proportional to the concentration of IL-6 in the sample. Results of both assays were read by 2 investigators (A.L.G., A.G.) in a blinded manner, and the similarity of results was 99%. A blood culture was performed in 88 (89%) children, a urine culture in 89 (90%), and a CSF culture in 17 (17%). Of 40 (40%) children who were hospitalized, 35 (88%) were treated with antibiotics, only by intravenous route, and among those sent home, antibiotics were prescribed for 36 (61%; 10 oral, 1 intramuscularly, and 25 intravenously). SBIs were diagnosed in 29 (29%) children and included 4 occult bacteraemia, 21 pyelonephritis, 2 lobar pneumonia, 1 mastoiditis, and 1 retropharyngeal abscess. *Streptococcus pneumoniae* and *Streptococcus agalactiae* were the causative organisms of 3 and 1 occult bacteraemia, respectively. *Escherichia coli* was the organism recovered from 90% of all urinary tract infections (UTIs). Benign infection was diagnosed in 70 (71%) children. Eleven subjects had lower UTI, 4 developed acute otitis media diagnosed at the follow-up visit, and 3 had aseptic meningitis. Fifty-two (52%) children

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>aged 7 days to 36 months, who had a rectal temperature ≥38 °C and no localizing signs of infection in their history or at physical examination were eligible.

Excluded from the study were children with fever lasting longer than 7 days, children who were treated with antibiotics during the 2 previous days, and those with known immunodeficiencies. Children were examined by a paediatric resident who took a complete history, performed a physical examination, recorded the degree and duration of fever, and determined a clinical score, according to McCarthy. All children had a WBC count with differential and a determination of CRP, PCT, and IL-6 values. Toxic-appearing children had a full sepsis workup, were admitted to the hospital, and were given parenteral antibiotics. Nontoxic-appearing children, from 1 week to 90 days of age or from 91 days to 36 months of age with fever 39 °C, had a urine collection by suprapubic aspiration, transurethral bladder catheterization, or midstream catch for analysis and culture. Blood was systematically</td><td>were considered as having a probable viral infection based on negative bacterial cultures and no sign of a focal infection (except non-bloody diarrhoea) at the clinical follow-up visit.

Table : Sensitivity, Specificity, and Predictive Values of Markers of SBI

<table><tr><th></th><th>Sensitivity (% [95% CI])</th><th>Specificity (% [95% CI])</th><th>NPV (%)</th><th>PPV (%)</th><th>Relative Risk</th></tr><tr><td>PCT (ˣ0.5 ng/mL)</td><td>93 (77–99)</td><td>74 (62–84)</td><td>96</td><td>60</td><td>15</td></tr><tr><td>CRP (*40 mg/L)</td><td>79 (60–92)</td><td>79 (67–88)</td><td>90</td><td>61</td><td>6.1</td></tr><tr><td>Leukocytes ≥15 G/L</td><td>52 (33–71)</td><td>74 (62–84)</td><td>78</td><td>45</td><td>2.05</td></tr><tr><td>Band ≥1.5 G/L</td><td>11 (2–28)</td><td>93 (84–98)</td><td>72</td><td>38</td><td>0.74</td></tr><tr><td>Leukocytes ≥15 G/L or band ≥1.5 G/L</td><td>55 (36–74)</td><td>72 (61–83)</td><td>80</td><td>46</td><td>2.3</td></tr><tr><td>IL-6 (ˣ100 pg/L)</td><td>36 (13–65)</td><td>80 (64–91)</td><td>77</td><td>38</td><td>1.36</td></tr><tr><td>YOS score >10</td><td>23 (5–54)</td><td>82 (67–92)</td><td>76</td><td>30</td><td>1.25</td></tr></table>

Table :Demographic Characteristics and Laboratory Parameters of Children With Benign and Serious Bacterial Infection.

<table><tr><th></th><th>Benign Infection (Median [Range])</th><th>SBI (Median [Range])</th><th>P</th></tr><tr><td>Age (mo)</td><td>7.2 (0.4–31.1)</td><td>9.7 (0.7–34)</td><td>NS</td></tr><tr><td>Sex (M/F)</td><td>39/31</td><td>14/15</td><td>NS</td></tr><tr><td>Fever duration (h)</td><td>24 (1–140)</td><td>48 (6–140)</td><td>0.026</td></tr><tr><td>Fever (°C)</td><td>39.5 (38–40.8)</td><td>39.4 (38.3–41)</td><td>NS</td></tr><tr><td>PCT (</≥0.5 ng/mL)</td><td>52/18</td><td>2/27</td><td><0.01</td></tr><tr><td>CRP (mg/L)</td><td>16 (10–200)</td><td>100 (10–200)</td><td><0.01</td></tr><tr><td>IL-6 (</≥100 ng/L)</td><td>31/9</td><td>8/5</td><td>NS</td></tr><tr><td>Leukocytes (G/L)</td><td>10.2 (3–29.3)</td><td>15.1 (3.8–46.4)</td><td><0.01</td></tr></table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>cultured in children with leukocytes >15 g/L or band counts >1.5 g/L. In children from 91 days to 36 months of age with fever ≥38 °C but <39 °C, urine and blood culture were not performed unless biological risk factors (leukocytes >15 g/L, band counts >1.5 g/L, or leukocyturia) were present. A spinal tap was performed when meningitis was suspected. Erythrocyte, platelet, and WBC counts were performed in blood samples mixed with ethylenediaminetetraacetic acid (EDTA) using an automated cell counter. Band form was counted manually by trained technicians. CRP value was determined in 50 µL of EDTA-blood with a rapid (15 minutes) immunometric method (Nycocard CRP) according to the instructions of the manufacturer. Procalcitonin was measured by a rapid semiquantitative immunochromatographic test .

Definition and criteria of SBIs were 1) bacteraemia, positive blood culture; 2) pyelonephritis, positive urine culture with >10^5 colony-forming units/mL and cortical defect seen at the technetium</td><td>
<table>
<tr><td>Band (G/L)</td><td>0.2 (0–2.7)</td><td>0.7 (0–13)</td><td><0.01</td></tr>
</table>

Combination of PCT (>0.5 ng/mL) and CRP (>40 mg/L) increased the sensitivity to 97% but decreased the specificity to 61% (data not shown). Among the 29 children with SBI, 2 had a PCT concentration below the limit of detection of the test (<0.5 ng/mL). One had occult pneumococcal bacteraemia and came to the ED with a fever lasting <10 hours. The second case had pyelonephritis with minimal but positive changes at the DMSA renal scintigraphy. Six (6%) and 14 (14%) children with SBI had a CRP value <40 mg/L and a leukocyte count <15 G/L, respectively.

Table :Likelihood Ratios (LR) for selected range of values of PCT, CRP, and Leukocyte Counts and Post-test Probability of SBI in Children With FWS
<table>
<tr><td></td><td>n</td><td>LR (95% CI)</td><td>Post-test Probability (%)</td></tr>
<tr><td>PCT</td><td></td><td></td><td></td></tr>
<tr><td><0.5 ng/mL</td><td>54</td><td>0.09 (0.02–0.36)</td><td>3</td></tr>
<tr><td>0.5–2</td><td>26</td><td>2.8 (1.49–5.33)</td><td>54</td></tr>
<tr><td>>2</td><td>19</td><td>5.2 (2.20–12.42)</td><td>68</td></tr>
<tr><td>CRP</td><td></td><td></td><td></td></tr>
<tr><td><40 mg/L</td><td>61</td><td>0.26 (0.13–0.54)</td><td>10</td></tr>
<tr><td>40–100</td><td>22</td><td>2.0 (1.04–4.01)</td><td>45</td></tr>
<tr><td>>100</td><td>16</td><td>14.5 (3.46–60.70)</td><td>86</td></tr>
<tr><td>Leukocyte</td><td></td><td></td><td></td></tr>
<tr><td><15 G/L</td><td>66</td><td>0.65 (0.44–0.97)</td><td>21</td></tr>
<tr><td>15–20</td><td>15</td><td>1.6 (0.63–4.11)</td><td>40</td></tr>
<tr><td>>20</td><td>18</td><td>2.4 (1.07–5.46)</td><td>49</td></tr>
</table>
</td></tr>
</table>

Citation/EL	Method	Results
	99M-dimercaptosuccinic acid (DMSA) renal scintigraphy; 3) lobar pneumonia, lobar consolidation diagnosed on a chest radiograph by a paediatric radiologist unaware of the study; 3) bacterial meningitis, cerebrospinal fluid (CSF) pleocytosis of >5 cells/µL and positive culture of CSF; 4) deep abscess, assessed by computed tomography scan and surgical exploration. Children were classified as having a benign infection for the purpose of this study on the basis of 1) negativity of blood or CSF culture, 2) positive urine culture with a normal DMSA renal scintigraphy, 3) clinical improvement without antibiotics, and 4) the presence of a focal infection at the follow-up visit such as otitis media or gastroenteritis.	
Carrol[166] Study type: prospective cohort EL: II	Country: UK Aim: This study aimed to determine whether PCT might be a useful marker of MCD in children presenting with fever	There were 108 children in total included. In 64 children (group I), a clinical diagnosis of MCD was made in an ill child with fever and a petechial or purpuric rash (probable cases), in all of whom the diagnosis was confirmed microbiologically. These children were all managed as cases of MCD, and were notified to the consultant in communicable disease control. In 44 children (group II), all microbiological tests were negative for MCD, and the supervising clinician made an alternative diagnosis (see table below). These children were all initially thought to have MCD, not just fever and petechiae. The ROC plot of the relative accuracies of CRP and PCT in differentiating MCD from other illnesses in children presenting with fever and a rash. The areas under the curve (AUC) for CRP and PCT, at the given thresholds, were 0.90 (95% CI 0.83 to 0.97) and 0.96 (95% CI 0.90 to 1.00) respectively. The proportion difference between these AUCs is not statistically different from zero (95% CI -0.012 to 0.14, p

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>and a rash, and to compare this with CRP and WCC. Additionally, we aimed to determine if there was any correlation between PCT and the pro-inflammatory cytokines TNFα, IL-6, and IL-8.

Setting, inclusion/ exclusion:

From September 1992 to April 1994 and November 1997 to March 1999, Children (0–15.9 years) were included in the study if they were referred to the meningococcal research fellow at the Royal Liverpool Children's Hospital NHS Trust, Alder Hey with a presumptive diagnosis of MCD, from two prospective studies.

PCT, WCC, and CRP were measured on samples which had been taken on admission and stored at -70 °C.

In children with a clinical diagnosis of MCD, severity of disease was assessed using the Glasgow Meningococcal Septicaemia Prognostic Score (GMSPS). Severe disease was defined as a GMSPS of ≥8. Concentrations of TNFα, IL-6, and IL-8 were also determined on plasma samples taken on admission. The plasma samples were stored at -70 °C until assayed</td><td>= 0.11).

Table : Median (interquartile range) age, PCT, and CRP concentrations in groups I and II
<table>
<tr><th></th><th>Group I</th><th>Group II</th><th>p value*</th></tr>
<tr><td>Age (y)</td><td>3.57 (1.19–8.22)</td><td>1.75 (0.82–5.28)</td><td>0.02</td></tr>
<tr><td>WCC (x10^9/l)</td><td>10.44 (3.50 –21.58)</td><td>11.24 (7.90–17.40)</td><td>0.62</td></tr>
<tr><td>PCT (ng/ml)</td><td>38.85 (11.26–75.63)</td><td>0.27 (0.23-0.76)</td><td><0.0005</td></tr>
<tr><td>CRP (mg/l)</td><td>68.35 (38.20–111.50)</td><td>9.25 (5.18–18.00)</td><td><0.0005</td></tr>
<tr><td colspan="4">* Mann-Whitney test</td></tr>
</table>

There was no significant difference in duration of symptoms between the two groups. There was no significant correlation between PCT and CRP and duration of symptoms. There was a significant negative correlation between admission calcium and PCT (r = -0.597, p < 0.0005), but a positive correlation with CRP (r = 0.393, p = 0.015). There was a significant positive correlation between PCT and TNFα (r = 0.473, p < 0.0005) and IL-8 (r = 0.575, p < 0.0005) but not IL-6 (r = 0.222, p = 0.078)F. There was a negative correlation between CRP and TNFα (r = -0.415, p = 0.001) and IL-8 (r = -0.314, p = 0.012), but no correlation with IL-6 (r = -0.177, p = 0.163).

In group I, 37 children (57.8%) had severe disease, and five (7.8%) died. PCT was significantly higher in those with severe disease (p = 0.001); it was higher in those who died, but this difference was not significant (p = 0.299).

Table :Performance characteristics of WCC, CRP, and PCT
<table>
<tr><th></th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>PPV (%)</th><th>NPV (%)</th><th>Relative Risk</th></tr>
<tr><td>Procalcitonin >2 ng/ml</td><td>94 (90–98)</td><td>93 (88–98)</td><td>95 (91–99)</td><td>91 (86–96)</td><td>10.6 (0.38-24.8)</td></tr>
<tr><td>CRP >30 mg/l</td><td>81 (74–88)</td><td>89 (83–95)</td><td>91 (86–96)</td><td>76 (68–84)</td><td>3.79 (2.7-6.0)</td></tr>
<tr><td>WCC <4 or >15 x 10^9/l</td><td>69 (60–78)</td><td>67 (58–76)</td><td>77 (69–85)</td><td>56 (46–66)</td><td>1.67 (1.28-2.5)</td></tr>
<tr><td>Procalcitonin >2 ng/ml and CRP >30 mg/l</td><td>80 (72–88)</td><td>95 (91–99)</td><td>96 (92–100)</td><td>76 (68–84)</td><td>4.0 (2.9-6.25)</td></tr>
<tr><td colspan="6">95% confidence intervals in parentheses.</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>using an enzyme amplified sensitivity immunoassay.</td><td></td></tr>
<tr><td>Kohli[168]

Study type :
prospective cohort study
EL: II</td><td><u>Country:</u>
India
<u>Aim:</u>
To examine the value of serum C-reactive protein (CRP) in febrile children without an apparent focus of infection, (i) as a tool to differentiate bacteraemia and bacterial infection from a non-bacterial illness (NBI), and (ii) as an indicator of recovery or complications.
<u>Setting, inclusion/ exclusion:</u>
From March 1989 and August 1990, children 3 mo to 3 years with a temperature of >= 38.5 °C, without an apparent focus. A normal chest x-ray and a peripheral blood film negative for malaria parasites were included in the Paediatric Emergency Unit of Nehru Hospital. The serum CRP concentration was measured on days 1, 3 and 5 of evaluation and correlated with the final diagnosis and outcome.
The urine was cultured in all cases, and the CSF analysed and cultured in all infants < 1</td><td>They included 98 children (53 boys and 45 girls; mean age 11.7 mo; SD: 8.5 mo; 63% < 1 yr.).The serum CRP was 40 mg/l and above in 95% of patients (18/19) with bacteraemia and also in seven of the eight with purulent meningitis, while it was < 40 mg/l in 84% of patients (52/62) with NBI (mean (SD) 22 (28.6) mg/l). The mean serum CRP concentration among six children with a culture-positive urinary tract infection (16.3 (8.3) mg/l) and five with otitis media (9 (5.7) mg/l) was similar to those with NBI. The sensitivity of serum CRP >= 40 mg/l for diagnosis of bacteraemia was 95% and the positive predictive value 67%.

Table :Specificity, sensitivity, and predictive values of total leukocyte count (TLC), mESR, temp and CPR in detecting bacteraemia

<table>
<tr><td></td><td>Sensitivity %</td><td>Specificity%</td><td>PPV %</td><td>NPV %</td><td>RR*</td></tr>
<tr><td>TLC ≥15000/mm3</td><td>20</td><td>100</td><td>100</td><td>82</td><td>5.56</td></tr>
<tr><td>ESR>25mm/hr</td><td>63</td><td>95</td><td>86</td><td>90</td><td>8.6</td></tr>
<tr><td>Tem ≥39 °C</td><td>26</td><td>96</td><td>66</td><td>82</td><td>3.67</td></tr>
<tr><td>TLC>=15000 and/or ESR > 25</td><td>74</td><td>92</td><td>74</td><td>92</td><td>9.25</td></tr>
<tr><td>TLC ≥15000 and/32 or temp ≥39 °C</td><td>68</td><td>80</td><td>52</td><td>89</td><td>4.73</td></tr>
<tr><td>CRP- quantitative</td><td>32</td><td>96</td><td>67</td><td>82</td><td>3.72</td></tr>
<tr><td>Serum CRP</td><td>100</td><td>62</td><td>43</td><td>100</td><td>--</td></tr>
<tr><td>Serum CRP ≥ 40µg/l</td><td>95</td><td>86</td><td>67</td><td>98</td><td>33.5</td></tr>
<tr><td colspan="6">*: Calculated from provided info.</td></tr>
</table>

The serum CRP concentration showed a decline in all 18, the mean) concentrations on days 1,3 and 5 being 98 (SD:49), 40 (SD:25) and 19 (SD:11) mg/l, respectively. In 15 of 19 cases, the fall in serum CRP occurred12-36 hr before a decline in temperature. In another three, the decline in temperature and CRP was simultaneous.</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>y, and in older children when indicated. Patients with an underlying neoplastic or immunosuppressive condition or with a chronic disease (e.g. nephritic syndrome, or liver or heart disease) were excluded.</td><td></td></tr>
<tr><td>Pulliam[169]

Study type:
Prospective cohort study.

EL:II</td><td>Country:
USA
Aim:
To determine the diagnostic properties of quantitative C-reactive protein (CRP) associated with clinically undetectable serious bacterial infection (SBI) in febrile children 1 to 36 months of age.
Setting, inclusion/ exclusion:
A convenience sample of children ages 1 to 36 months who presented to the duPont Hospital for Children Emergency Department (ED) with temperature >=39 °C were evaluated by residents and paediatric emergency medicine attendings.
Children with acute otitis media, acute pharyngitis, clinical pneumonia, acute respiratory tract infection, acute gastroenteritis, and those with a history of antibiotic use during the past 7</td><td>Seventy-seven children were enrolled in the study ranging in age from 1 to 35 months (mean: 9.7 months; standard deviation [SD]: 8.0). Fourteen patients (18%) had SBI and 63 had no SBI. Causes of SBI included UTI (6), pneumonia (4), 1 of whom also had bacteraemia, and OB (4). Escherichia coli was the causative organism of all UTI’s and Streptococcus pneumoniae was the organism recovered from the 5 cases of bacteraemia.
Table : Characteristics of Children With and Without SBI
<table>
<tr><th>Characteristic*</th><th>Patients With SBI (n = 14)</th><th>Patients Without SBI (n = 63)</th><th>P Value</th></tr>
<tr><td>Age (mo)</td><td>10.6 (9.3)</td><td>9.5 (7.8)</td><td>0.64</td></tr>
<tr><td>Sex (% female)</td><td>71.4</td><td>52.4</td><td>0.19</td></tr>
<tr><td>Temperature in ED (°C)</td><td>39.5 (0.74)</td><td>39.5 (0.73)</td><td>0.99</td></tr>
<tr><td>Duration of fever, median (range), h</td><td>24 (3, 168)</td><td>24 (1, 168)</td><td>0.24</td></tr>
<tr><td>Total YOS</td><td>8.9 (3.8)</td><td>8.6 (3.8)</td><td>0.77</td></tr>
<tr><td>WBC (1000/mm^3)</td><td>22.3 (9.8)</td><td>12.5 (7.0)</td><td>0.003</td></tr>
<tr><td>Polymorphonuclear cells (%)</td><td>56.3 (7.6)</td><td>52.5 (15.3)</td><td>0.19</td></tr>
<tr><td>Band count (%)</td><td>5.7 (5.8)</td><td>3.6 (4.2)</td><td>0.11</td></tr>
<tr><td>ANC (1000/mm^3)</td><td>13.9 (6.1)</td><td>7.3 (5.4)</td><td><.0001</td></tr>
<tr><td>CRP concentration, median (range) mg/dL</td><td>9.7 (0.2, 37.2)</td><td>1.0 (0.2, 20.7)</td><td>0.002</td></tr>
</table>
* Values shown are means ±SD unless otherwise noted.</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>days, a known underlying immunologic disease, or who received vaccination during the previous 2 days were excluded. Demographic information, i.e., age and sex, ED temperature, duration of fever, and clinical evaluation using the Yale Observation Score (YOS) were recorded at the time of initial evaluation. Total WBC, band count, ANC, and quantitative CRP concentration were obtained. All patients received a blood culture and either a screening urinalysis or urine culture. Urine was obtained by urethral catheterization using standard sterile technique. Chest radiographs as well as other laboratory and radiographic tests were obtained at the discretion of the ED physician.

The outcome result was the presence of laboratory or radiographically proven SBI (bacteraemia, meningitis, UTI, pneumonia, septic arthritis, and osteomyelitis). OB was defined on the basis of recovery of a single bacterial pathogen using standard culture techniques. UTI was defined as growth of a single urinary tract pathogen at ≥10^4 CFU/mL. Pneumonia was defined as the presence of a</td><td>The diagnostic properties of WBC, ANC, and CRP concentration were analyzed using the receiver operating characteristic curve. The area under the ROC curve was 0.905 (standard error [SE]: 0.05; 95% CI: 0.808, 1.002) for CRP concentration and 0.805 (SE: 0.051; 95% CI: 0.705, 0.905) for ANC. The AUC for WBC was 0.761 (SE: 0.068; 95% CI: 0.628, 0.895).

Table : Predictors of SBI
<table>
<tr><th>Variable</th><th>Cut-off Point</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>Likelihood Ratio (95% CI)</th><th>PPV (95% CI)</th><th>NPV (95% CI)</th><th>Relative (95%CI)</th></tr>
<tr><td>WBC (1000/mm^3)</td><td>15.0</td><td>64 (35.8, 85.9)</td><td>67 (53.6, 77.7)</td><td>1.9 (1.1, 3.1)</td><td>30 (14.7, 49.4)</td><td>89 (76.9, 96.5)</td><td>2.73 (0.64-1</td></tr>
<tr><td>ANC (1000/mm^3)</td><td>10.2</td><td>71 (42.2, 90.3)</td><td>76 (63.6, 85.6)</td><td>3.0 (1.7, 5.1)</td><td>40 (21.1, 61.3)</td><td>92 (81.5, 97.9)</td><td>5 (1.14-29.2</td></tr>
<tr><td>CRP concentration (mg/dL)</td><td>7.0</td><td>79 (49.0, 94.2)</td><td>91 (79.8, 96.0)</td><td>8.3 (3.8, 27.3)</td><td>65 (38.3, 85.8)</td><td>95 (86.1, 99.0)</td><td>13(2.76-85.8</td></tr>
</table>
Three patients with SBI had CRP concentrations <7 mg/dL, 1 with UTI (age 1 month, CRP 6.8 mg/dL, duration of fever 6 hours), 1 with pneumonia (4 months old, CRP 5.4 mg/dL, duration of fever 8 hours), and 1 with OB (4 months old, CRP 0.2 mg/dL, duration of fever 3 hours).

Table : Multilevel Likelihood Ratios for CRP Concentration
<table>
<tr><th>CRP Concentration (mg/dL)</th><th>Likelihood Ratio (95% CI)</th><th>Post-test Probability of SBI</th></tr>
<tr><td>>9</td><td>9.0 (3.2, 25)</td><td>67%</td></tr>
<tr><td>7–9</td><td>6.8 (1.4, 31)</td><td>60%</td></tr>
<tr><td>5–7</td><td>1.8 (0.42, 7.0)</td><td>29%</td></tr>
<tr><td><5</td><td>0.087 (0.02, 0.38)</td><td>1.9%</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>focal infiltrate on chest radiograph as interpreted by the paediatric radiologist.</td><td></td></tr>
<tr><td>Galetto-Lacour[245]

study type:
prospective cohort study
EL: II</td><td>Country:
Switzerland
Aim:
To examine whether the determination of procalcitonin (PCT), interleukin (IL)-6, IL-8 and interleukin-1 receptor antagonist (IL-1Ra) was superior to these commonly used markers for the prediction of a serious bacterial infection (SBI).
Setting, inclusion/ exclusion:
From March 1998-August 1999.
Children, 7 days to 36 months of age, with a rectal temperature above 38 °C and without localising signs of infection were prospectively enrolled in the Department of Pediatrics, University Hospital Geneva. For each infant, they performed a physical examination, a clinical score according to McCarthy, a complete white cell count, an urine analysis and a determination of CRP. We further determined PCT, IL-6,</td><td>A total of 124 children were included of whom 28 (23%) had SBI. Concentrations of PCT, CRP and IL-6 were significantly higher in the group of children with SBI but IL-8 and IL-1Ra were comparable between both groups. PCT showed a sensitivity of 93% and a specificity of 78% for detection of SBI and CRP had a sensitivity of 89% and a specificity of 75%.
Table :Comparisons of different parameters and the mean concentrations of the indicators between children with benign infections and SBI.
<table>
<tr><th></th><th>Benign infection (n=96)</th><th>SBI (n=28)</th><th>p</th></tr>
<tr><td>Age (mo)</td><td>10.9±0.9</td><td>11.2±1.8</td><td>ns</td></tr>
<tr><td>Fever duration (h)</td><td>24 (1-240)</td><td>27 (2-140)</td><td>0.02</td></tr>
<tr><td>Temp (°C)</td><td>39.0±0.1</td><td>39.1±0.2</td><td>Ns</td></tr>
<tr><td>PCT (ng/ml)</td><td>0.40(0.11-43.3)</td><td>3.6(0.25-364)</td><td><0.01</td></tr>
<tr><td>CRP (mg/l)</td><td>20 (10-200)</td><td>108 (10-200)</td><td><0.01</td></tr>
<tr><td>IL-6 (pg/l)</td><td>14.7 (1.5-801)</td><td>69 (10-801)</td><td><0.01</td></tr>
<tr><td>IL-8 (pg/l)</td><td>ND(ND-3869)</td><td>43.5 (ND-145)</td><td>Ns</td></tr>
<tr><td>II-1Ra</td><td>5173(435-74868)</td><td>8381(689-49917)</td><td>Ns</td></tr>
</table>
Sensitivity, specificity, PPV and NPV of different markers for the predictions of a SBI.
<table>
<tr><th></th><th>Sensitivity % (95% CI)</th><th>Specificity % (95% CI)</th><th>PPV %</th><th>NPV %</th><th>Relative Risk</th></tr>
<tr><td>PCT (0.9ng/ml)</td><td>93 (77-99)</td><td>78 (69-86)</td><td>55</td><td>97</td><td>18.33</td></tr>
<tr><td>CRP (40mg/dl)</td><td>89 (72-98)</td><td>75 (65-83)</td><td>51</td><td>96</td><td>12.75</td></tr>
<tr><td>Leukocytes >15000/mm3</td><td>68 (48-84)</td><td>77 (67-85)</td><td>46</td><td>89</td><td>4.18</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>IL-8, and IL-1Ra concentrations and compared their predictive value with those of the usual management of fever without localising signs. Each infant at risk of SBI had blood culture, urine and cerebrospinal fluid cultures when indicated, and received antibiotics until culture results were available.</td><td>
<table>
<tr><td>Band 1500/mm3</td><td>29 (13-49)</td><td>91 (83-96)</td><td>46</td><td>81</td><td>1.59</td></tr>
<tr><td>YOS >10</td><td>20 (3-56)</td><td>86 (76-93)</td><td>29</td><td>79</td><td>1.38</td></tr>
<tr><td>IL-6 (50pg/l)</td><td>79 (59-92)</td><td>66 (55-75)</td><td>40</td><td>91</td><td>4.44</td></tr>
<tr><td>IL-1 RA (9500 pg/l)</td><td>71 (51-87)</td><td>63 (52-72)</td><td>36</td><td>88</td><td>3.0</td></tr>
<tr><td>IL-8 (9500 pg/l)</td><td>38 (15-65)</td><td>79 (69-87)</td><td>34</td><td>81</td><td>23.0</td></tr>
<tr><td>PCT (0.9 pg/l) or CRP (40 mg/l)</td><td>96 (82-100)</td><td>67 (56-76)</td><td>46</td><td>98</td><td>13.0</td></tr>
<tr><td>PCT (0.9 pg/l) or Leukocytes >15000/mm3</td><td>100 (88-100)</td><td>62 (51-71)</td><td>43</td><td>100</td><td>--</td></tr>
</table>

Table :Sensitivity, specificity, PPV and NPV for a SBI of PCT and CRP in relation to age
<table>
<tr><th></th><th>Age (mo)</th><th>Sensitivity %</th><th>Specificity %</th><th>PPV %</th><th>NPV%</th><th>Relative Risk</th></tr>
<tr><td>PCT (0.9ng/ml)</td><td><12(n=80)</td><td>94</td><td>87</td><td>68</td><td>98</td><td>34</td></tr>
<tr><td></td><td>>12(n=44)</td><td>90</td><td>62</td><td>41</td><td>96</td><td>10.3</td></tr>
<tr><td>CRP (40mg/dl)</td><td><12(n=80)</td><td>94</td><td>84</td><td>63</td><td>98</td><td>31.5</td></tr>
<tr><td></td><td>>12(n=44)</td><td>80</td><td>59</td><td>36</td><td>91</td><td>4.0</td></tr>
</table>
</td></tr>
<tr><td>Isaacman[170]

study type:
prospective cohort study

EL: II</td><td>Country:
USA.
Aim:
To assess the utility of serum C-reactive protein (CRP) as a screen for occult bacterial infection in children.
Setting, inclusion/ exclusion:
Children visiting the emergency department of Children's Hospital of The</td><td>Two hundred sixty-six patients (age range: 3-36 mo. The median age: 15.3 months (range, .3.1-35.2 months) were enrolled in the study, and 9 were later found to have undetected exclusion criteria and were subsequently excluded (8 with antibiotic use within 48 hours and 1 with known bacteraemia within 48 hours). One additional patient was analyzed separately because of a history of immunodeficiency. The median temperature at triage was 40.0 °C (range, 39.0 °C-41.3 °C); median length of illness was 24 hours (range, 0-288 hours). Twenty-nine patients (11.3%) had OBI: 17 with pneumonia, 9 with a urinary tract infection, and 3 with bacteraemia. The immunocompromised patient did not have an OBI, and since comparisons based on one subject have questionable validity, the patient was excluded from analysis. No significant demographic or clinical difference was detected between those included in the study and those excluded from analysis. Comparing patients with OBI with those without, neither age nor length of illness were significantly different (for age and length of illness, P = 0.51, and P =0 .10, respectively); however, median temperature in triage was significantly higher for those with OBI (P = .04).

Table : Demographic and clinical comparisons
<table>
<tr><th>Features</th><th>OBI</th><th>Non-OBI</th><th>Excluded</th></tr>
</table>
</td></tr>
</table>

Citation/EL	Method	Results

King's Daughters (Norfolk, Va), a free-standing, urban children's hospital, who were between 3 and 36 months of age were eligible for participating this study. The determination as to whether a CBC and blood culture were drawn, as well as other laboratory testing (including urinalysis and culture and chest radiograph), was made by the paediatric emergency medicine attending physician who was supervising the patient. Patients were excluded if they had taken any oral or parenteral antibiotics within 48 hours of the visit, or had a known case of bacteraemia during the previous 48 hours. Immunodeficient patients were enrolled, but analyzed separately. C-reactive protein levels were measured using a heterogeneous immunoassay format; normal values using this assay are 0 to 0.9 mg/dL. House staff and attending staff were informed that CRP levels were being analyzed for study purposes only. Data recorded on each patient included age, temperature in triage, length of existing febrile illness (in hours), history of antibiotic use in the past 48 hours, and

Age (mo)	13.5 (4.3-33.6)	15.5 (3.1-35.2)	19.7 (5.3-26.1)
Temp (°C)	40.2 (39.0-41.2)	40.0 (39.0-41.3)	39.7 (39.0-40.6)
Length of illness	24 (4-240)	24 (0-288)	24 (12-96)
WBC (thousands)	19.7 (6.4-39.1)	11.4 (3.6-33.9)	9.0 (4.8-26.2)
CRP	5.6 (0.7-43.3)	1.5 (0.2-31.1)	2.7 (1.2-7.8)
ANC	13.8 (2.6-26.4)	6.6 (0.6-28.2)	4.9 (1.3-17.6)
Note : All data are presented as mean (range).			

Due to the biological rise and decay rate of CRP, the timing of presentation was included in regression models. This is of special interest since most patients in our study group, 219 overall (81%), and 25 of those with OBI (81%), came to the emergency department for treatment 12 or more hours after the onset of illness. No significant difference was detected in the distribution of CRP levels between patients presenting within 12 hours of onset of illness compared with at least 12 hours after illness. The sensitivity of CRP to detect OBI among patients seen at least 12 hours after onset of illness only slightly exceeds that for patients seen within 12 hours (0.68 vs. 0.67, respectively), with a proportional drop in specificity (0.81 vs. 0.85, respectively).

Three (1.1%) of the 256 analyzed study patients had occult bacteraemia; there were 2 cases of *Streptococcus pneumoniae* bacteraemia, and 1 case of *Salmonella* infection. To ensure that the prevalence of occult bacteraemia mirrored that in our overall emergency department, we reviewed the microbiology reports from of all children 3 to 36 months of age who had a blood culture done during the period from February 2000 to February 2001. Seventeen hundred seventy-two cultures were drawn during this year; there were 38 pathogens (2.1%) and 38 contaminants (2.1%). A comparison between the bacteraemia rates in the study population vs. the overall emergency department population revealed that there was no significant difference (*P* = 0.26).

Table : Comparisons of the diagnostic accuracy of WBC, CRP, ANC and combinations of those.

Test	Cut off values	AUC (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Relative Risk (95%CI)*
WBC	17.1	0.69 (0.61-077)	0.69 (0.51-0.89)	0.80 (0.75-0.85)	0.31 (0.20-0.43)	0.95 (0.92-0.98)	6.2 (0.025-0.215)
CRP	4.4	0.71 (0.62-0.79)	0.63 (0.43-0.82)	0.81 (0.76-0.87)	0.30 (0.18-0.3)	0.94 (0.91-0.98)	5.0 (0.02-0.15)
ANC	10.6	0.73 (0.65-0.81)	0.69 (0.51-0.89)	0.79 (0.73-0.84)	0.32 (0.20-0.44)	0.95 (0.91-0.98)	6.4 (0.02-0.22)

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>history of immunodeficiency.

Blood cultures were processed using the Bactec F system (Beckton Dickinson Diagnostics, Sparks, Md) with constant surveillance for 5 days. Results of total WBC, ANC, and CRP levels were recorded and used to compute the sensitivity, specificity, and positive and negative predictive values of these results with the outcome of interest—OBI. Occult bacterial infection was defined as bacteraemia, pneumonia, or urinary tract infection in which no focal abnormalities were evident on physical examination. Bacteraemia was defined as growth of a pathogen in blood culture.

The diagnosis of "occult pneumonia" was based on a radiologic diagnosis of lobar infiltrate or pneumonia in a patient with no abnormalities noted on physical examination. Urinary tract infection was defined as 10^4 or more colony-forming units per cubic millilitre of a single organism in a catheterized urine specimen, or 10^5 or more colony-forming units per cubic millilitre of a single organism from a bagged</td><td>
<table>
<tr><td>WBC or CRP</td><td>17.1
≥3.1</td><td>0.63 (0.53-0.71)</td><td>0.76 (0.59-0.92)</td><td>0.58 (0.51-0.64)</td><td>0.19 (0.12-0.27)</td><td>0.95 (0.91-0.99)</td><td>3.8 (1.33-0.27)</td></tr>
<tr><td>ANC or CRP</td><td>10.5
≥3.6</td><td>0.66 (0.57-0.74)</td><td>0.79 (0.64-0.95)</td><td>0.50 (0.43-0.56)</td><td>0.17 (0.10-0.23)</td><td>0.95 (0.91-0.99)</td><td>3.4 (0.01-0.23)</td></tr>
<tr><td colspan="8">*: calculated form provided info.</td></tr>
</table>

Two multiple logistic regression models were fit that included age, temperature, length of illness, CRP, and either ANC (model 1) or WBC (model 2). Backward elimination identified only ANC (or WBC), CRP, and length of illness as independent predictors of OBI. In the first model, each cell increase of 1000 x 10^9/L in the ANC resulted in a risk increase of 1.15 for OBI (OR = 1.15; 95% CI, 1.07-1.24; P<0.001) after adjusting for CRP and length of illness. Each 1-mg/dL increase in CRP resulted in a risk increase of 1.12 for OBI (OR = 1.12; 95% CI, 1.04-1.20; P =0.003), adjusting for ANC and length of illness. Similarly, each 1-hour increase in length of illness resulted in a risk increase of 1.01 for OBI (OR = 1.01; 95% CI, 1.00-1.03; P =0.01), adjusting for ANC and CRP. In the second model, each cell increase of 1000 x 10^9/L in the WBC resulted in a 1.15 risk increase for OBI (OR = 1.15; 95% CI, 1.07-1.23; P<.001) after adjusting for CRP and length of illness. Each 1-mg/dL increase in CRP resulted in a 1.12 increase in risk of OBI (OR = 1.12; 95% CI, 1.04-1.21; P =0.003), adjusting for WBC and length of illness. Similarly, each 1-hour increase in length of illness resulted in a risk increase of 1.01 for OBI (95% CI, 1.00-1.02; P =0.05), adjusting for WBC and CRP.</td></tr>
</table>

Citation/EL	Method	Results
	specimen.	
Fernandez[171] Study type: prospective cohort study. EL: II	Country: Spain Aim: To evaluate the utility of PCT in distinguishing between viral and bacterial infections in febrile children in the ED, comparing PCT with CRP and the rest of the parameters used up to now (total leukocyte and total neutrophil count); to determine the diagnostic performance of PCT and CRP in detecting invasive infections and differentiating them from non-invasive infections; To compare both markers in the group of infants with evolution of fever <12 h; and to assess the utility of the BRAHMS PCT-Q semiquantitative rapid test in the febrile child. Setting, inclusion/ exclusion: This was a prospective, multicenter (9 hospitals) study conducted in the paediatric ED of the participating hospitals between April 2000 and March 2001. The study included children between 1 and 36 months of age treated for fever	Patient characteristics The patients were distributed in four groups corresponding to viral infections (Group 1), localized bacterial infections (Group 2), invasive bacterial infections (Group 3) and control group (Group 4). Group 1 was composed of children with fever of viral aetiology without evidence of bacterial superinfection and with negative bacterial cultures (blood, urine and cerebrospinal fluid culture if lumbar puncture was performed). Respiratory infections (caused by respiratory syncytial virus, adenovirus and parainfluenza virus) were diagnosed by means of direct immunofluorescence in nasopharyngeal secretions, and serologic techniques were used to confirm the aetiology of Epstein-Barr and herpes type 6 viruses. The detection of herpes simplex virus in cerebrospinal fluid was by polymerase chain reaction, and enterovirus meningitis was demonstrated by culture. Immunochromatographic tests in faeces confirmed the aetiology of enteritis caused by rotavirus and adenovirus. The localized infections group included bacterial tonsillitis infections (demonstrated by culture or rapid test), peritonsillar abscesses caused by *Streptococcus pyogenes* with negative blood culture, acute otitis media infections verified by the Otorhinolaryngology Department, mastoiditis and/or otoantritis without osteitis (diagnosed by computerized axial tomography), bacterial acute gastroenteritis infections without systemic involvement in children >3 months of age and lower urinary tract infections (>50 000 colonies of a single microorganism in a urine sample obtained by bladder probe). The following were considered as potentially invasive or severe bacterial diseases: meningitis infections confirmed by a positive culture of cerebrospinal fluid; sepsis confirmed by microbiologic analysis; bone or joint infections confirmed by local isolation or in blood culture of the microorganism; acute pyelonephritis infections; lobar pneumonia; bacterial enteritis in infants <3 months; and occult bacteraemia. The differentiation between acute pyelonephritis and lower urinary tract infections was determined by renal gammagraphy with dimercaptosuccinic acid, which enabled the differential diagnosis to be made upon revealing a lesion in the renal parenchyma. The control group comprised children in the same age group who were given a blood test for reasons unrelated to infectious disease and who met none of the exclusion criteria. The study included 445 children with a mean age of 12.9 months (SD 9.9) and a range of 1 to 36 months. The viral infections group (*n* = 122) was composed of bronchiolitis cases (caused by respiratory syncytial virus, adenovirus and parainfluenza virus) without bacterial superinfection, gastroenteritis caused by rotavirus, infections caused by the Epstein-Barr virus, meningoencephalitis caused by the herpes simplex virus and infections caused by the herpes zoster and herpes type 6 viruses. All infants with viral infections had PCT values of <0.7 ng/ml (range, 0.08 to 0.6 ng/ml); CRP values fluctuated between <3 mg/l and 121.5 mg/l. Moreover 22.5% of the viral infections had CRP values higher than 20 mg/l. The localized bacterial infection group (*n* = 80) included lower urinary tract infections, gastroenteritis in children >3 months of age and otorhinolaryngeal infections. In this group the PCT and CRP mean values were 0.38 mg/l (SD 0.52) and 35.2 ng/ml (SD 41.4), respectively. The invasive infection group included children with acute pyelonephritis caused by *Escherichia coli,* sepsis caused by *Neisseria meningitidis* and *E. coli,* meningitis caused by *Streptococcus pneumoniae*, arthritis caused by *Salmonella* spp., osteomyelitis caused by *Staphylococcus aureus* and lobar pneumonia, among other infections. Group 4 was made up of 93 children of age comparable with those of the other three groups (mean, 16.76 months; SD 10.44). The PCT and CRP values in the control group were 0.15 ng/ml (SD 0.12) and 3 mg/l (SD 2.5), respectively, and were significantly lower than those in the other groups. Mean PCT and CRP values for bacterial infections were higher than those for viral infections. The area under the curve for PCT and CRP was 0.82 (SD 0.02) and 0.78 (SD 0.02), respectively. The optimum cut-off value for PCT for distinguishing between viral and bacterial infections was 0.53 ng/ml (sensitivity, 65.5%; specificity, 94.3%). For CRP the optimum cut-off value in our sample was 27.5 mg/l (sensitivity, 63.5%; specificity, 84.2%). The PCT specificity was higher than that of CRP for distinguishing between viral and

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>in paediatric ED and who were required to undergo blood analysis to rule out the possibility of bacterial infection. These children also required hospital admission.

Fever was defined as the presence of an axillary temperature >=38 °C. The temperature reading was taken in the emergency room with a mercury thermometer for at least 3 min. The following were considered as exclusion criteria for potential study subjects: (1) antibiotic treatment in the 48 h before admission to the hospital; (2) vaccination in the days before the study, which may have caused the febrile syndrome; (3) surgery performed in the 7 days before inclusion in the study; (4) any chronic pathology that could alter CRP values (rheumatic disease, intestinal inflammatory disease or other causes); and (5) a history of prior urinary infection, pathology involving malformation of the kidney or of the urinary tract and vesicoureteral reflux.

Blood samples were obtained for routine tests (complete blood count, CRP and culture), and for each patient included</td><td>bacterial infections, but the diagnostic performance differences were not statistically significant. If we consider only Groups 2 (localized bacterial infection) and 3 (invasive bacterial infection), PCT obtained a better diagnostic performance for differentiating between both groups. The area under the curve for PCT was 0.93 (SD 0.01) and 0.74 (SD 0.03) for CRP (P < 0.001).

If only consider Groups 2 (localized bacterial infection) and 3 (invasive bacterial infection), PCT obtained a better diagnostic performance for differentiating between both groups. The area under the curve for PCT was 0.93 (SD 0.01) and 0.74 (SD 0.03) for CRP (P < 0.001).

Children with invasive bacterial infections presented decreased level of consciousness and worse general condition more often and were significantly older than the non-invasive infection group. The rest of the clinical parameters did not make it possible to distinguish between both groups at the time of the examination in the emergency room. The figures for total leukocytes, total neutrophils and immature neutrophils in blood analyses were significantly higher in the invasive bacterial infections group. although its diagnostic performance was very low. The area under the curve obtained was 0.65 (SD 0.03) for total leukocytes and 0.68 (SD 0.03) for total neutrophils with very low sensitivity (54 and 54.9%, respectively). Mean PCT and CRP values in invasive bacterial infections were statistically higher than those for non-invasive infections (p<0.001), but the diagnostic performance of PCT was better according to the analysis.

The area under the curve for PCT was 0.95 (SD 0.01), significantly higher (P :0.001) than that obtained for CRP (0.81; SD 0.02). In our study the optimum cut-off value for PCT in detecting invasive infections was >0.59 ng/ml (sensitivity, 91.3%; specificity, 93.5%); for CRP it was >27.5% mg/l (sensitivity, 78%; specificity, 75%). The positive and negative predictive values were also

higher for PCT.

Table :ROC curves for CRP and PCT for differentiation between invasive (Group 3) and non-invasive (Groups 1 + 2) infections. Comparison with the area under the curve and diagnostic performance for leukocytes and total neutrophils.
<table>
<tr><td></td><td>PCT</td><td>CRP</td><td>Leukocyte</td><td>Total neutrophil</td></tr>
<tr><td>Area</td><td>0.82 (0.02)</td><td>0.78 (0.02)</td><td>0.65 (0.03)</td><td>0.69 (0.03)</td></tr>
<tr><td>Optimal cut-off</td><td>PCT>0.53 ng/ml</td><td></td><td>Leukocytes 16500/mm^3</td><td></td></tr>
<tr><td></td><td>Sensitivity: 65.5%</td><td>PPV: 95.5%</td><td>Sensitivity: 50.9%</td><td>PPV: 81.8%</td></tr>
<tr><td></td><td></td><td>NPV: 59%</td><td></td><td>NPV: 45.6%</td></tr>
<tr><td></td><td>Specificity: 94.3 (%)</td><td>RR: 2.33</td><td>Specificity: 79.2%</td><td>RR: 1.50</td></tr>
<tr><td>Optimal cut-off</td><td>CPR>27.5 mg/l</td><td></td><td>Neutrophils > 9576/mm^3</td><td></td></tr>
<tr><td></td><td>Sensitivity: 63.5%</td><td>PPV: 88.5%</td><td>Sensitivity: 49.8%</td><td>PPV: 86%</td></tr>
</table>
</td></tr>
</table>

Citation/EL	Method	Results
	in this study a serum sample was frozen for later determination of the procalcitonin level. In 176 cases PCT and PCT-Q values were determined from the blood tests requested by the paediatrician in the ED on making up the plasma or serum of this sampling without involving additional blood volume. In the rest an additional amount was extracted in the same sampling carried out in the emergency room, which in no case exceeded 0.5 ml of blood. PCT values were determined in duplicate by the LUMItest PCT immunoluminometric analysis, which uses two specific monoclonal antibodies and requires 20 µl of serum or plasma. The CRP was obtained by the immunoturbidimetry procedure. PCT and CRP values of <=0.5 ng/ml and 15 mg/l, respectively, were considered normal. The semiquantitative rapid test used was the BRAHMS PCT-Q test, which required 250 µl of serum or plasma and uses a monoclonal mouse anti-calcitonin antibody conjugated	NPV: 54.9% NPV: 44% Specificity: 84.2% RR: 1.97 Specificity: 83.3 % RR: 1.54 All the children with sepsis and meningitis (*n* = 66) had PCT >0.6 ng/ml even in the first analysis conducted in the ED (range, 0.7 to 500 ng/ml); in 17 cases the CRP values were <27.5 mg/l (range, 2 to 260 ng/l). Patients with acute pyelonephritis showed mean PCT levels of 4.9 ng/ml (SD 13.2; range, 0.1 to 79.6 ng/ml), whereas the maximum PCT value in lower urinary tract infections was 1 ng/ml (mean, 0.28; SD: 0.20). Conversely 9 patients with acute pyelonephritis had normal CRP (< 15 mg/l), and 5 of these patients had high PCT values, between 0.7 and 36 ng/ml. Eleven children with normal renal gammagraphy had CRP of >30 mg/l, but PCT values were <0.5 ng/ml in 9. The mean evolution of fever time was 32.8 h (SD:38.6) with a range of 1 to 255 h. No statistically significant differences were found in fever evolution time between the groups compared which could have affected the results obtained. In children with evolution of fever earlier than 12 h (*n* = 104), the mean PCT value in the invasive infections group was also significantly higher than in the non-invasive group. The statistical significance was lower for CRP, and no differences were found in the total leukocyte count. In this group the area under the curve for PCT was 0.93 (SD: 0.03), which was significantly greater ($P < 0.001$) than that obtained for CRP (0.69; SD:0.05). In the cases the optimum cut-off value for PCT in detecting invasive bacterial infections in these patients was 0.69 ng/ml (sensitivity, 85.7%; specificity, 98.5%); for CRP this value was >19 mg/l (sensitivity, 61.3%; specificity, 80%). Table : ROC curves for CRP and PCT for differentiation between invasive (Group 3) and non-invasive (Groups 1 + 2) infections in infants with fever evolution of <12 h. PCT CRP Area 0.93 (0.03) 0.69 (0.05) Optimal cut-off PCT>0.69 ng/ml Sensitivity: 85.7% PPV: 96.9% NPV: 89.7% Specificity: 98.5 % RR: 9.41 Optimal cut-off CPR>19 mg/l Sensitivity: 61.3% PPV: 65.8% NPV: 76.5% Specificity:80% RR: 2.8 For detection of invasive bacterial infections, the PCT-Q test achieved sensitivities and specificities of 90.6 and 83.6%, respectively (with positive and negative predictive values of 80.8 and 92.2%)

Citation/EL	Method	Results
	with colloidal gold (tracer) and a polyclonal sheep anti-calcitonin antibody (solid phase).	
Gendrel[172] Study type: prospective cohort study. EL:II	Country: France Aim: To identify a marker capable of distinguishing between bacterial and viral infections in children with fever admitted to hospital as emergency cases Setting, inclusion/ exclusion: This study was carried out between January 1, 1995, and April 1, 1997.During this period 1500 children between 1 month and 15 years of age were admitted to the hospital with a body temperature >38.5 °C. PCT was determined on admission for 700 of these children. Procalcitonin was systematically determined after informing the parents and the child. It was determined on a sample of the congealed plasma remaining after all the routine biologic tests (including CRP determination) ordered by the doctor in charge of emergencies in our hospital had been done. The plasma remaining after procalcitonin	The causal agent of the infectious syndrome was identified for 360 of the 700 children for whom PCT was determined on admission. These patients formed the study group. They were assigned to three categories according to the nature of the infection. *Group 1: Invasive bacterial infections (*n = *46).* This group consisted of 23 children admitted to hospital for bacterial meningitis and 23 others admitted for septicaemia (positive blood culture on admission). The mean age of the children in this group was 2.1 years (range, 1 month to 7 years) and the infectious agents in for these cases are reported. *Group 2: Localized bacterial infections (*n = *78).* This group consisted of 78 children with negative blood culture results for whom a bacterium detected in a specimen was identified as the most probable cause of infection. The mean age of the children in this group was 4.2 years (range, 2 months to 15 years). Eighteen of these children were admitted for pneumonia, thought to be bacterial based on radiographic images and the detection of *Streptococcus pneumoniae* (11 cases) or *Haemophilus influenzae* (3 cases) in pure or almost pure cultures obtained from rhinopharyngeal or sputum samples. Four other patients had *Mycoplasma* pneumonia, as demonstrated by serologic tests. *Group 3: Viral infections (*n = *236).* A viral infection was diagnosed in 236 patients (mean age, 2.2 years; range, 1 month to 15 years). A virus was detected by immunofluorescence or culture in 141 children. PCR with the probes detected enterovirus mRNA in the cerebrospinal fluid samples of 64 children admitted for lymphocytic meningitis. In 31 cases viral infection was demonstrated by a large increase (3-fold or greater rise) in the antibody titre between 2 samples taken 2 weeks apart, with no possible bacterial cause identified. PCT was determined not only for the 360 children from whom a pathogen was isolated but also for 22 patients with high fever admitted to hospital for other identified illnesses. Systemic inflammatory diseases, with body temperature >38.5 °C, were diagnosed in 10 patients and malaria caused by *Plasmodium falciparum* in 12 others. **Procalcitonin.** Of the 46 children in Group 1 (96%) 44 had procalcitonin values >2 µg/l. These 44 children were treated with antibiotics either immediately, based on clinical signs, or after the results of cerebrospinal fluid analysis were obtained. Two of the children in this group had positive blood cultures and low PCT on admission. One was a 12-month-old child with moderate acute otitis media, and the other was a 9-month-old child with diarrhoea caused by *Salmonella typhimurium.* The PCT values of these 2 children were 0.15 and 0.3 µg/l, respectively. Neither of the 2 children was judged to be in a serious clinical state requiring antibiotic treatment on admission, but both had received ambulatory antibiotic treatment for 2 days before admission to hospital. Of the 70 children in Group 2, 59 had PCT concentrations >1 µg/l. Three of the 19 patients with PCT levels <1 µg/l had urinary tract infections and were treated with antibiotics after examination of urine samples. Eight were admitted to hospital for bacterial diarrhoea. None of these 8 patients received antibiotics on admission, and only 2 patients were treated with antibiotics during their hospital stay. Seven others, younger than the age of 2 years, had bronchiolitis (RSV isolated from the throats of 3 patients) with a pulmonary focus identified radiologically and bacteria (*S. pneumoniae* or *H. influenzae*) isolated from rhinopharyngeal samples. Four of these 7 patients were treated with antibiotics on admission, based on clinical and radiologic symptoms. The other 3 received antibiotic treatment 2 or 3

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>determination was used to determine IFN-α and then IL-6.

Only included those children for whom the responsible pathogen was identified. Patients with known chronic disease were excluded. All patients were admitted to the hospital based on clinical examinations at the request of the hospital emergency team who did not know the result of the tests for PCT, IL-6 or IFN-α.</td><td>days after admission.

Of the 59 patients in Group 2 with PCT > 1 µg/l, 20 had urinary infections and were given antibiotic treatment on admission. Of the remaining 39 patients 30 were given antibiotics on admission and 5 received antibiotics on the following days. Four were not treated (2 cases of diarrhoea caused by Salmonella sp., 1 case of diarrhoea caused by Campylobacter jejuni and 1 case of moderate acute otitis media).

Of the 236 patients in group with viral infections 13 had procalcitonin concentrations between 1 and 2 µg/l and only 3 patients had procalcitonin values >2 µg/l. The maximum concentration of procalcitonin observed was 5.2 µg/l, in a 6-year-old child with Epstein-Barr virus infection, who had macrophage activation syndrome.

<u>C-reactive protein.</u> In Group 1, 5 of the 46 children (10.8%) with septicaemia or bacterial meningitis had CRP concentrations <20 mg/l. In Group 2, 15 of the 78 children (19.2%) had CRP values <20 mg/l. In Group 3, 111 of the 236 virus-infected children (47%) had CRP concentrations >10 mg/l and 61 (25.9%) had CRP concentrations >20 mg/l. With the exceptions of adenovirus and Epstein-Barr virus, all viruses had similar effects, increasing CRP concentrations in similar proportions. Eight of the 9 children infected with Epstein-Barr virus and 7 of the 11 infected with adenovirus had CRP concentrations >20 mg/l.

PCT with a cut-off value of 1 µg/l provided the best compromise between sensitivity (0.83) and specificity (0.93) for distinguishing between bacterial and viral infections. This test, with this cut-off, was clearly better than any other combination (see table 4) The calculated positive predictive value was accurate, indicating that only 14% of subjects with a PCT concentration of 1 mg/l or above were false positives. Higher positive predictive values were achieved with higher cut-off scores, but at the expense of lower sensitivity. Higher positive predictive values would be expected for lower cut-off scores in populations with a higher prevalence of bacterial infection.

Table : Prognostic values for selected cut-off points in the discrimination between bacterial (Group 1+2) and Viral infections (Group 3)
<table>
<tr><th>Test & cut-off</th><th>Sensitivity %</th><th>Specificity%</th><th>PPV%*</th><th>NPV%*</th><th>RR%</th></tr>
<tr><td>PCT>1µg/l</td><td>83</td><td>93</td><td>86</td><td>91</td><td>9.6</td></tr>
<tr><td>PCT>2µg/l</td><td>65</td><td>99</td><td>97</td><td>85</td><td>6.47</td></tr>
<tr><td>PCT>3µg/l</td><td>57</td><td>99</td><td>97</td><td>82</td><td>5.39</td></tr>
<tr><td>CRP>10ng/l</td><td>98</td><td>50</td><td>50</td><td>98</td><td>25</td></tr>
<tr><td>CRP>20ng/l</td><td>83</td><td>71</td><td>60</td><td>89</td><td>5.45</td></tr>
<tr><td>CRP>30ng/l</td><td>73</td><td>88</td><td>76</td><td>86</td><td>5.43</td></tr>
<tr><td>IL-6>200pg/ml</td><td>51</td><td>85</td><td>64</td><td>77</td><td>2.78</td></tr>
<tr><td>IFN-α=0</td><td>92</td><td>79</td><td>69</td><td>95</td><td>13.8</td></tr>
</table></td></tr>
</table>

Citation/EL	Method	Results

Table continued:

	25%PPV**	25%NPV**	RR25%	50%PPV**	50%NPV**	50%RR
PCT>1µg/l	80	94	13.3	92	85	6.13
PCT>2µg/l	96	89	8.73	98	74	3.77
PCT>3µg/l	95	87	7.31	98	70	3.27
CRP>10ng/l	40	99	40.0	66	96	16.5
CRP>20ng/l	49	93	7.0	74	81	3.89
CRP>30ng/l	67	91	7.44	86	77	3.74
IL-6>200pg/ml	53	84	3.31	77	63	2.08
IFN-α=0	59	97	19.7	81	91	9.0

*: PPVs and NPVs in study sample (prevalence of bacterial infection 34%).

**: PPVs and NPVs when the prevalence of bacterial infection is 25% and 50%.

For distinguishing between invasive bacterial infections (Group 1) and localized bacterial or viral infections (Groups 2 + 3), PCT with a cut-off point of 2 µg/l gave the best compromise between sensitivity (0.96) and specificity (0.87). This test, with this particular cut-off point, was clearly better than any other combination (see table 5). The negative predictive value was very high, indicating that only 0.7% of the subjects with PCT concentrations of 2 mg/l were false negatives.

Prognostic values for selected cut-off points in the discrimination between invasive bacterial (Group 1) and bacterial localised plus Viral infections (Group 2+3)

Test & cut-off	Sensitivity %	Specificity%	PPV%	NPV%	RR
PCT>1µg/l	96	76	37	99	37
PCT>2µg/l	96	87	52	99	52
PCT>3µg/l	91	90	58	99	58
CRP>10ng/l	98	38	19	99	19
CRP>20ng/l	89	58	24	97	8

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>CRP>20ng/l</td><td>87</td><td>75</td><td>34</td><td>98</td><td>17</td></tr>
<tr><td>IL-6>200pg/ml</td><td>79</td><td>80</td><td>37</td><td>96</td><td>9.25</td></tr>
<tr><td>IFN-α=0</td><td>96</td><td>65</td><td>29</td><td>99</td><td>29</td></tr>
</table>
</td></tr>
<tr><td>Lembo[173]

<u>Study type:</u>
Prospective cohort study.
EL:II</td><td><u>Country:</u>
USA
<u>Aim:</u>
To determine whether quantification of serum CRP is of value in assessing the risk of bacterial meningitis in febrile infants and children to the ED.
<u>Setting, inclusion/ Exclusion:</u>
From February 1984 to August 1985, children presenting to the ED or Acute Care of the Cleveland Metropolitan General Hospitals for evaluation of an acute fever episode. Patients were enrolled if after a complete history and physical examination, the managing physician decided that bacterial meningitis could be the source of fever or if the child was less than 2 months old and was to have CSF obtained as part of a standard “sepsis workup”.
Patients were excluded if they had a history of malignancy, immunodeficiency, or</td><td>Children were stratified by the history or physical exam findings at presentation:
Children in the absent symptom group had a history of irritability and poorly consoled crying, lethargy, or headache or still neck.
Children in the positive physical sign group had meningitis signs (nuchal rigidity and Kerning’s or Brudzinski’s signs) or signs of increased intracranial pressure; whereas the absence of all these features constituted the absent physical sign group.
During the study period, 392 febrile children had lumbar puncture. Sufficient sera were available for quantification of CRP from 163 patients (42%). Of 163 children available for study, 10 (6%) had bacterial meningitis, of the remaining 153, 14 had aseptic meningitis , 10 had culture-documented extra-meningeal source of bacterial infection.
Table :Diagnostic accuracy of individual variable
<table>
<tr><th></th><th>No</th><th>Sensitivity %</th><th>Specificity %</th><th>PPV %</th><th>NPV %</th><th>RR</th></tr>
<tr><td>Meningitis signs</td><td>35</td><td>70</td><td>81</td><td>20</td><td>98</td><td>10</td></tr>
<tr><td>Symptoms</td><td>135</td><td>100</td><td>17</td><td>7</td><td>100</td><td>Infinity</td></tr>
<tr><td>CRP>1.0mg/dl</td><td>75</td><td>80</td><td>55</td><td>11</td><td>98</td><td>2.3</td></tr>
<tr><td>TPWBC>15000/mm^3</td><td>56</td><td>40</td><td>64</td><td>7</td><td>94</td><td>1.17</td></tr>
</table>
Stepwise logistic regression analysis indicated that meningeal signs and CRP level in the serum were the best predictors of bacterial meningitis. details see table below.
Results of stepwise logistic regression analysis modelling among signs, symptoms, acute phase reactants and bacterial meningitis.
<table>
<tr><th>Variable</th><th>X^2</th><th>P</th></tr>
<tr><td>Meningitis signs</td><td>8.83</td><td>0.003*</td></tr>
<tr><td>Symptoms</td><td>2.71</td><td>0.099*</td></tr>
<tr><td>CRP>1.0mg/dl</td><td>1.15</td><td>0.283</td></tr>
<tr><td>TPWBC>15000/mm^3</td><td>0.43</td><td>0.512</td></tr>
</table>
*: two-variables (X^2 =14.7; p=0.006)
They found that ten out of 89 children with either meningeal signs or a CRP level > 1.0mg/dl had bacterial meningitis compared with none of 71 children with meningeal signs absent and a CRP level of 1.0mg/d or less (p=0.003).</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>intracranial surgery or were receiving immunosuppressive therapy.

The number of children attending to ED with fever not reported. All patients underwent lumbar puncture.

<u>Material meningitis</u> was defined on the basis of the recovery of a bacterial pathogen from CSF by standard culture techniques or by the identification of specific bacterial antigen in combination with a positive Gram stain of CSF in the absence of a positive culture. Aseptic meningitis was defined on the basis of a CSF pleocytosis (more than 10 total nucleated cells / mm^3 with less than 1000 RBC/ $mm^{3.}$ sterile cultures of blood and CSF, and a negative CSF Gram stain and bacterial antigen.</td><td>Relationships among signs alone, the combination of signs and CRP and bacterial meningitis in all children.

<table>
<tr><th>Variable</th><th>Bacterial meningitis</th><th>Other illness</th><th>Total</th></tr>
<tr><td>Meningeal signs present</td><td>7 (20%)</td><td>28 (80%)*</td><td>35</td></tr>
<tr><td>Meningeal signs absent</td><td>3 (2%)</td><td>122 (98%)*</td><td>125</td></tr>
<tr><td>Signs present and/or CRP>1.0mg/dl</td><td>10 (11%)</td><td>79 (89%)**</td><td>89</td></tr>
<tr><td>Signs absent and/or CRP<=1.0mg/dl</td><td>0 (0)</td><td>71 (100%)**</td><td>71</td></tr>
</table>
Total number: 160

*: p=0.001 by exact test, sensitivity:70%; specificity: 81%

** p=0.02 by exact test, Signs present and CRP>1.0mg/dl sensitivity:100%; specificity: 47%, PPV: 11%, NPV: 100%, RR: infinity.

Relationships among symptoms alone, the combination of symptoms and CRP and bacterial meningitis in children without meningeal signs.

<table>
<tr><th>Variable</th><th>Bacterial meningitis</th><th>Other illness</th><th>Total</th></tr>
<tr><td>Symptoms present</td><td>3 (3%)</td><td>99(97%)*</td><td>102</td></tr>
<tr><td>Symptoms absent</td><td>0 (0)</td><td>23 (100%)*</td><td>23</td></tr>
<tr><td>Symptoms present and CRP>1.0mg/dl</td><td>3 (7%)</td><td>42 (93%)**</td><td>45</td></tr>
<tr><td>Symptoms absent and/or CRP<=1.0mg/dl</td><td>0 (0)</td><td>80 (100%)**</td><td>80</td></tr>
</table>
Total number: 125

*: p=1.00 by exact test, sensitivity:100%; specificity: 19%; PPV &NPV not reported.

** p=0.04 by exact test, Symptoms present and CRP>1.0mg/dl: sensitivity:100%; specificity: 66%, PPV:7%; NPV: 100% RR: infinity.</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td>Galetto-Lacour[178]

study type:
prospective cohort study
EL:II</td><td>Country:
Switzerland
Aim:
Whether the determination of procalcitonin (PCT), interleukin (IL)-6, IL-8 and interleukin-1 receptor antagonist (IL-1Ra) was superior to these commonly used markers for the prediction of a serious bacterial infection (SBI).
Method and Inclusion/ exclusion:
From March 1998 to August 1999. Children aged 7 days to 36 months of age consulting the ED of the University Children’s Hospital of Geneva with a rectal temperature above 38 degrees and without localising signs of infection were prospectively enrolled. Each was examined by a paediatric resident who took a complete history, performed a physical exam, recorded height and duration of fever and McCarthy’s Observation scale. Children with fever lasting for > 7days, neonates < 1week and all children treated with antibiotics in the previous 2 days as well as those with known immunodeficiency were excluded.</td><td>A total of 133 children were included. Nine of them were excluded because they did not present at clinical follow-up or suffered from immunodeficiency (number not specified). Together 124 patients were analyzed.
A total of 124 children were included of whom 28 (23%) had SBI. Concentrations of PCT, CRP and IL-6 were significantly higher in the group of children with SBI but IL-8 and IL-IRa were comparable between both groups.
Table :Summary table of the comparison of different parameters and the mean concentrations of PCT, CRPIL-6, IL-8and IL-1Ra between children with benign infections and SBIs.
<table>
<tr><th>Age (mo)</th><th>Benign infection (n=96)</th><th>SBI (n=28)</th><th>P</th></tr>
<tr><td>Fever duration (hr)</td><td>10.9+-0.9</td><td>11.2+-1.8</td><td>Ns</td></tr>
<tr><td>Temperature (c)</td><td>24 (1-240)</td><td>27 (2-140)</td><td>0.02</td></tr>
<tr><td>PCT (ng/ml)</td><td>39.0+-0.1</td><td>39.1+-0.2</td><td>Ns</td></tr>
<tr><td>CRP (mg/l)</td><td>0.40 (0.11-43.3)</td><td>3.6 (0.25-364)</td><td><0.01</td></tr>
<tr><td>IL-6 (pg/l)</td><td>14.7(1.5-801)</td><td>69 (10-801)</td><td><0.01</td></tr>
<tr><td>LI-8 (pg/l)</td><td>ND (ND-3869)</td><td>43.5 (ND-145)</td><td>Ns</td></tr>
<tr><td>II-1Ra (pg/l)</td><td>5173 (435-74868)</td><td>8381 (689-49917)</td><td>Ns</td></tr>
</table>
Given as mean +- SE or median and range.
IL-8 values were below the detection level (40 pg/ml) in 50 subjects with a benign infection and in 7 subjects with a serious infection.
ND: not detectable.
The other parameters used routinely not shown in the table above (total and differential leukocyte count, McCarthy score) had lower sensitivity ranging from 20-68% (details not given).
Table :Values of different markers for the perdition of SBI.
<table>
<tr><th></th><th>Sensitivity (95%CI)</th><th>Specificity (95%CI)</th><th>NPV(%)</th><th>PPV(%)</th><th>RR</th></tr>
<tr><td>PCT (0.9 ng/ml)*</td><td>93 (77-99)</td><td>78 (69-86)</td><td>97</td><td>55</td><td>18.3</td></tr>
<tr><td>CRP (40 mg/l)*</td><td>89 (72-98)</td><td>75 (65-83)</td><td>96</td><td>51</td><td>12.75</td></tr>
<tr><td>Leukocytes>15000/mm^3</td><td>68 (48-84)</td><td>77 (67-85)</td><td>89</td><td>46</td><td>4.18</td></tr>
<tr><td>Band >1500/mm^3</td><td>29 (13-49)</td><td>91 (83-96)</td><td>81</td><td>46</td><td>2.42</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>They performed a physical examination, a clinical score according to McCarthy, a complete white cell count, a urine analysis and a determination of CRP on each infant. All children had a clinical follow-up with physical examination by a paediatrician within the following 48 hours or by telephone contact. The diagnosis was registered at the end of the clinical follow-up. Each infant at risk of SBI had blood culture, urine and cerebrospinal fluid cultures when indicated, and received antibiotics until culture results were available.</td><td>
<table>
<tr><td>McCarthy Score>10</td><td>20 (3-56)</td><td>86 (76-93)</td><td>79</td><td>29</td><td>1.38</td></tr>
<tr><td>IL-6(50pg/l)*</td><td>79 (59-92)</td><td>66 (55-75)</td><td>91</td><td>40</td><td>4.44</td></tr>
<tr><td>IL-1Ra (950pg/l)*</td><td>71 (51-87)</td><td>63 (52-72)</td><td>88</td><td>36</td><td>3.0</td></tr>
<tr><td>IL-8(70pg/l)</td><td>38 (15-65)</td><td>79 (69-87)</td><td>81</td><td>34</td><td>1.79</td></tr>
<tr><td>PCT (0.9 ng/ml)* or CRP (40 mg/l)</td><td>96 (82-100)</td><td>67 (56-76)</td><td>98</td><td>46</td><td>23.0</td></tr>
<tr><td>PCT (0.9 ng/ml)* or Leukocytes>15000/mm^3</td><td>100 (88-100)</td><td>62 (51-71)</td><td>100</td><td>43</td><td>--</td></tr>
</table>
*: cut-off level.

Table : Values for SBI of PCT and CRP in relation to age
<table>
<tr><th></th><th>Age (mo)</th><th>Sensitivity(%)</th><th>Specificity (%)</th><th>NPV(%)</th><th>PPV(%)</th><th>RR</th></tr>
<tr><td>PCT (0.9 ng/ml)*</td><td><12(n=80)</td><td>94</td><td>87</td><td>98</td><td>68</td><td>34.0</td></tr>
<tr><td></td><td>>12(n=44)</td><td>90</td><td>62</td><td>96</td><td>41</td><td>10.25</td></tr>
<tr><td>CRP (40 mg/l)*</td><td><12(n=80)</td><td>94</td><td>84</td><td>98</td><td>63</td><td>31.5</td></tr>
<tr><td></td><td>>12(n=44)</td><td>80</td><td>59</td><td>91</td><td>36</td><td>4.0</td></tr>
</table>
*: cut-off level.

The likelihood ration for a positive PCT was 4.24 (95% CI: 2.58-5.90) and for a positive CRP was 3.57 (95% CI:2.25-4.89).
</td></tr>
<tr><td>Lee[175]

study type:
prospective cohort study

EL: II</td><td>Country:
USA
Aim:
There are two aims: 1) to determine the prevalence of occult bacteraemia in a cohort of febrile children 3 to 36 months of age after the introduction of the Haemophilus influenzae type b</td><td>They had 199868 patient visits to the ED from January 1, 1993, to December 31, 1996. Children between the ages of 3 and 36 months accounted for 70142 of the patient visits (35%) to the ED. No temperature was recorded for 2193 children (3%) and these patients were excluded from the study. Of the remaining children who were 3 to 36 months of age, 15912 (23%) had a temperature of 39.0 °C. After excluding patients, 11911 patients remained who were considered at risk for occult bacteraemia. The 3 most common diagnoses were otitis media (n=4200), fever (n=3228), and unspecified viral infection (n=2896).

Of these 11911 patient visits to the ED, 8974 (75%) had a complete blood cell count done and 8782 (74%) had a differential cell count performed. A manual differential cell count was performed in 7471 (63%) and an automated differential cell count was completed in the remainder of patients. Blood cultures were drawn in 9465 (79%) of the patient visits. Blood cultures were less likely to be drawn when a diagnosis of otitis media was made (71% vs. 84%, P<0.01). Of 246 blood cultures from which organisms were isolated, 149 were considered pathogens: S pneumoniae in 137 (92%), Salmonella species in 7 (5%), N meningitidis in 2 (1%), group A streptococci in 2 (1%), and group B streptococci in 1 (1%). Haemophilus influenzae type b was not isolated from the blood of any of these children. The</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>conjugate vaccine and 2) to provide data from which to assess the risk of Streptococcus pneumoniae bacteraemia in well-appearing young children, so that proponents of antibiotic administration to selected febrile children are able to choose optimal criteria.

<u>Setting, inclusion/ exclusion:</u>

Patients treated in the ED between January 1, 1993, and December 31, 1996, were considered initially for inclusion in our study population of subjects at risk for occult bacteraemia if they were between 3 and 36 months of age and had a triage temperature of 39.0 °C or higher recorded in the ED by rectal or tympanic measurement. Subsequently, they excluded children who were (1) admitted to the hospital, transferred to another facility, or died during the visit; (2) discharged with a diagnosis of a specific viral infection (croup, bronchiolitis, varicella, Coxsackievirus, herpangina, or stomatitis); (3) diagnosed with a focal bacterial infection, other than otitis media (pneumonia, abscess, cellulitis, meningitis,</td><td>prevalence of occult bacteraemia in this population of 9465 children 3 to 36 months of age with a temperature of 39.0 °C or higher and no obvious source of infection is 1.57% with a 95% CI of 1.32%-1.83%. Of those children with positive findings on blood culture, the most common diagnoses were fever (n=78), otitis media (n=46), and unspecified viral infection (n=19). Occult bacteraemia occurred in 1.55% (95% CI: 1.11%-1.99%) of children with otitis media compared with 1.59% (95% CI: 1.28%-1.89%) of children without otitis media. The risk of occult pneumococcal bacteraemia alone is 1.45% (95% CI: 1.21%-1.69%). Occult pneumococcal bacteraemia occurred in 1.48% (95% CI: 1.05%-1.92%) and 1.43% (95% CI: 1.14%-1.72%) of children with and without otitis media, respectively. Because there was no significant difference between the groups, patients with otitis media were included in subsequent analyses. All subsequent analyses will focus on pneumococcal bacteraemia alone.

They also found an increased prevalence of bacteraemia at higher temperatures. When compared with the 39.0 °C to 39.4 °C temperature group, the 40.0 °C to 40.4 °C, 40.5 °C to 40.9 °C, and 41.0 °C to 42.0 °C temperature groups showed significantly higher risks for bacteraemia with ORs of 1.90 (95% CI: 1.13-3.21), 2.6 (95% CI: 1.5-4.5), and 3.7 (95% CI: 1.9-7.3), respectively.

Rates of bacteraemia also increased with increasing values of WBC, ANC, and ABC (figures were provided with no sufficient details). Univariate logistic regression for each of these variables showed significant association with occult pneumococcal bacteraemia (Pearson χ^2 probability for goodness of fit >0.99 for WBC, ANC, and ABC).

Receiver-operating characteristic curves were constructed for temperature, WBC, ANC, and ABC (shown as figure). The measured AUCs for WBC (0.88±0.01) and ANC (0.89±0.01) were significantly better than those for ABC (0.74±0.03) or temperature (0.62±0.03). There was no difference between the ROC curves for WBC and ANC (P=0.22), but both exhibited greater accuracy than the ROC curves for ABC or temperature (P<0.01).

Summary table of the rates of Bacteraemia at Different White Blood Cell Count (WBC) and Temperature Cut-offs

Temperature cut-off, °C. *
<table>
<tr><th>WBC cut-off x 10^9/L</th><th>39.0-39.4</th><th>39.5-39.9</th><th>40.0-40.4</th><th>40.5-40.9</th><th>>=41.0</th><th>Row totals</th></tr>
<tr><td>0-4.99</td><td>0/165(0.0)</td><td>0/190(0.0)</td><td>0/111(0.0)</td><td>0/57(0.0)</td><td>0/20(0.0)</td><td>0/543(0.0)</td></tr>
<tr><td>5-9.99</td><td>0/917 (0.0)</td><td>2/1034(0.2)</td><td>1/787(0.1)</td><td>0/431(0.0)</td><td>0/125(0.0)</td><td>3/3294(0.1)</td></tr>
<tr><td>10-14.99</td><td>1/788 (0.1)</td><td>4/830(0.5)</td><td>2/667 (0.3)</td><td>6/384(1.6)</td><td>2/113(1.8)</td><td>15/2785(0.5)</td></tr>
<tr><td>15-19.99</td><td>7/352(2.0)</td><td>9/400(2.2)</td><td>18/339(5.3)</td><td>10/220(4.5)</td><td>4/74(5.4)</td><td>48/1385(3.5)</td></tr>
<tr><td>20-24.99</td><td>6/111(5.4)</td><td>6/146(4.1)</td><td>11/136(8.1)</td><td>9/77(11.7)</td><td>2/33(6.1)</td><td>34/503(6.8)</td></tr>
<tr><td>25-29.99</td><td>5/36 (13.9)</td><td>1/47(2.1)</td><td>3/40(7.5)</td><td>2/30(6.7)</td><td>1/14(7.1)</td><td>12/167(7.2)</td></tr>
<tr><td>30-50</td><td>3/20 (15.0)</td><td>08/22(36.4)</td><td>0/16(0.0)</td><td>2/16(12.5)</td><td>2/8(25.0)</td><td>15/82(18.3)</td></tr>
<tr><td>Total</td><td>22/2389(0.9)</td><td>30/2669(1.1)</td><td>35/2096(1.7)</td><td>29/1215(2.4)</td><td>11/387(2.8)</td><td>127/8756(1.5)</td></tr>
</table></td></tr>
</table>

Citation/EL	Method	Results
	sinusitis, osteomyelitis, pyelonephritis, lymphadenitis, cholangitis, mastoiditis, impetigo, scarlet fever, streptococcal pharyngitis, or urinary tract infection); (4) known to have a chronic illness or known immunodeficiency that would alter the approach to febrile illness such as leukaemia, agranulocytosis, aplastic anaemia, arteritis, renal transplant, congenital heart anomalies, congestive heart failure, cystic fibrosis, human immunodeficiency virus infection, Lyme disease, Kawasaki disease, nephrotic syndrome, and sickle cell anaemia. Laboratory tests were performed as part of the ED visit in accordance with the standard protocol in the department for patients meeting risk criteria for occult bacteraemia. Children with otitis media were included because previous publications have documented a similar rate of occult bacteraemia regardless of the presence of otitis media. The data were analyzed with and without these children to confirm that this was true of our population. <u>Definition of infection:</u>	* Each cell reports the number f patients with +ve blood culture in the number, the total in the denominator, and the percentage in the parentheses. The number in this table is slightly different in the text as this table represents only those who both WBC and blood culture were obtained. Sensitivities and Specificities at Different Cut-off Values for the White Blood Cell Count (WBC)* WBC cut-off x 10^9/L | Sensitivity % | Specificity % | PPV % | Child above predictive value % >=5 | 1.00 (0.96-1.00) | 0.06(0.06-0.07) | 1.6(1.3-1.8) | 1.6 (1.3-1.8) >=10 | 0.98 (0.93-0.99) | 0.44(0.43-0.45) | 2.5(2.1-3.0) | 2.5(2.1-3.0) >=15 | 0.86 (0.78-0.91) | 0.77(0.76-0.77) | 5.1(4.2-6.1) | 5.1(4.2-6.1) >=16 | 0.77 (0.69-0.84) | 0.81(0.80-0.82) | 5.6(4.6-6.9) | 5.6(4.6-6.9) >=17 | 0.72 (0.64-0.80) | 0.84(0.84-0.85) | 6.4(5.2-7.9) | 6.4(5.2-7.9) >=18 | 0.64(0.55-0.72) | 0.87(0.86-0.88) | 6.8(5.5-8.4) | 6.8(5.5-8.4) >=19 | 0.56 (0.47-0.65) | 0.90(0.89-0.90) | 7.5(6.0-9.4) | 7.5(6.0-9.4) >=20 | 0.48(0.39-0.57) | 0.92(0.91-0.93) | 8.1(6.3-10.4) | 8.1(6.3-10.4) *(): 95% CIs ; NPV not specified. A total of 586 patients visited the ED in the 12 weeks represented by the first week of each month of 1996. Of these patients, 8 (1.4%) were found to have an incorrectly coded discharge diagnosis recorded in the computer database. Eighty-nine patients (15.2%) were recently or currently being treated with antibiotics and 1 patient had been immunized within the previous 48 hours.

Citation/EL	Method	Results
	True-positive cultures were defined as group A streptococci, group B streptococci, Haemophilus influenzae type b, Neisseria meningitidis, Salmonellae species, and Streptococcus pneumoniae. LABORATORY METHODS White blood cell counts were performed using Bayer Technicon H3 Systems (Bayer Diagnostic, Tarrytown, NY) equipment. Blood cultures were performed using a recommended 1 to 3 mL of blood in a BACTEC PEDS PLUS media bottle and were read visually and by BACTEC NR660 equipment or BACTEC PEDS PLUS/F culture media and the model BACTEC 9240 continuous-monitoring system(Becton Dickinson, Tarrytown, NY).	
John[267] study type: observational study EL: III	Country: India Aim: To correlate CSF-RP using a qualitative latex agglutination test with the conventional rapid diagnostic method- the Gram's stain in patients clinically diagnosed as having bacterial meningitis and	The 212 patients were categorized into four groups. Group I: patients with clinical and lab evidence of bacterial meningitis and partially treated bacterial meningitis (n=22; bacterial culture positive=20; culture negative=1). Group II: patients with clinical and lab evidence of encephalitis (n=11). Group III: patients with clinical and lab evidence of tuberculous meningitis (n=18). Group IV: patients with other CNS disorders (n=161) febrile convulsion (n=87)

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>partially treated bacterial meningitis, and to differentiate it from viral encephalitis, tuberculous meningitis, febrile convulsions, and other disorders of the CNS system in a paediatric population.

<u>Setting inclusion/exclusion:</u>

CSF was obtained in 212 patients aged 15 days to 12 years, admitted to the paediatric wards of St. John's Vani Vilas Hospital, Bangalore, with clinical features suggestive of meningitis (details not provided).

CSF specimens were collected by lumbar punctures within 2 hours of microscopy, biochemistry, bacterial culture and CRP determination.</td><td>epileptic convulsions (n=70)

intracranial haemorrhage (n=4)

Ten patients in group I had antibiotic prior to the initial CSF collection, and 8 out of those 10 had positive culture. Among those 8 positive culture samples, Gram's stain showed positive in two (25%), whereas CRP was positive in all 8 (100%) samples.

Summary table of the results of bacterial culture, CRP and Gram's stain of CSF patients in Group I
<table>
<tr><th>Bacterial isolates</th><th>Total no</th><th>CRP (no)*</th><th>Gram's stain (no)</th></tr>
<tr><td>Staph. aureus</td><td>6</td><td>4</td><td>4</td></tr>
<tr><td>H. influenzae</td><td>2</td><td>2</td><td>1</td></tr>
<tr><td>S. pneumoniae</td><td>3</td><td>3</td><td>1</td></tr>
<tr><td>E coli</td><td>3</td><td>3</td><td>1</td></tr>
<tr><td>Kleb enterobacter sp.</td><td>2</td><td>2</td><td>1</td></tr>
<tr><td>S typhi</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Ps aeruginosa</td><td>3</td><td>3</td><td>1</td></tr>
<tr><td>No organism</td><td>2</td><td>2</td><td>0</td></tr>
<tr><td>Total</td><td>22</td><td>20(91%)</td><td>10 (46%)</td></tr>
</table>
*: numbers indicate samples pf CSF positive for PRP and showing the presence of bacterial on Gram's stain. P<0.001 when CRP was compared with Gram's stain.

Two of those who had Staph. aureus were also clinically malnourished (not defined).

Summary table of the comparisons of CSF lab findings between Group I and IV.
<table>
<tr><th>Lab test</th><th>Group I</th><th>Group II</th><th>Group III</th><th>Group IV</th></tr>
<tr><td>Total count (cells/cmm)</td><td>670.5+-200.9 (60-3600)</td><td>10.25+-39.5 (10-460)</td><td>117.8+-22.2 (10-288)</td><td>4.5+-0.3 (0-16)</td></tr>
<tr><td>Polymorph (%)</td><td>55.2+-7.0 (5-96)</td><td>69.9+-6.3 (16-92)</td><td>16.4+-1.5 (0-30)</td><td>0.6+-0.2 (0-12)</td></tr>
<tr><td>Lymphocyte (%)</td><td>44.8+-7.0 (4-95)</td><td>30.0+-6.3 (8-84)</td><td>73.7+-5.4 (9-94)</td><td>8.6+-1.5 (0-92)</td></tr>
</table></td></tr>
</table>

Citation/EL	Method	Results
		Protein (mg%) 271.3+-26.7(110-490) 79.8+-15.3 (20-168) 216.3+-12.4 (110-300) 32.1+-0.9 (14-46) Glucose (mg%) 28.0+-2.3(20-48) 55.8+-5.0 (35-84) 31.0+-12.4 (<20-40) 59.7+-0.6 (48-75) Gram's stain 10(46%) 0 0 0 Positive CRP 20(91%) 0 0 0.6% The cell count in Group I was significantly higher than Group III (p<0.002) and Group IV(p<0.001). The protein was also higher in Group I compared to Group II (p<0.001) and Group IV (p<0.001). glucose level of Group I was decreased in relation to that of Group II (p<0.001) and Group IV (p<0.001). CRP to detect bacterial meningitis had sensitivity of 91%, specificity 99%, NPV: 99% and PPV 95%; RR: 95; other details not specified. CRP was positive in 91% (20/22) of Group I against Gram's stain which showed organism in 46% of patients (10/22).

Citation/ EL	Methodology	Effect size
Casado-Flores[268] EL: III Study type: prospective study. *EL III due to narrow population (PICU)*	Country: Spain Aim: To determine whether semi-quantitative procalcitonin (PCT-Q) measurements on admission can identify the severity of meningococcal infection in children. Setting, inclusion/ exclusion: This was an observational, prospective study of all patients with meningococcal infection in our paediatric *intensive care unit* from January 1998 to June 2003. The inclusion criteria were: (1)	A total of 65 patients (40 boys), mean age 2.4 years (range 2 months–9.25 years), met the inclusion criteria. A group of 33 patients presented with septic shock on admission, of whom 18 developed MODS. Mortality was 14% (*n* =9) and was preceded by shock and MODS in all cases. PCT-Q was >=10 ng/ml in 43 patients, between 2 and 9.9 ng/ml in 12, between 0.5–1.9 ng/ml in 6 and <0.5 ng/ml in 4. All patients with PCT-Q <10 ng/ml survived, whereas patients with PCT-Q >=10 ng/ml on admission frequently developed shock (26/43, *P* =0.03), MODS (18/43, *P* <0.001) or died (9/43, *P* =0.02). Only 7/33 patients presenting shock showed a PCT-Q of <10 ng/ml, and the shock rapidly remitted with standard fluid and dopamine therapy. Table : Meningococcal complications according to PCT-Q test levels in 65 children

PCT-Q (ng/ml)	Patients (*n*)	Shock	MODS	Death
>=10	43	26*	18**	9**
2–9.9	12	5	0	0
0.5–1.9	6	1	0	0
<0.5	4	1	0	0

<table>
<tr><th>Citation/ EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>Neisseria meningitidis in blood and/or CSF and (2) clinical manifestations consistent with acute meningococcal infection (rapid onset of disease, fever, purpura and shock) during an epidemic outbreak of N. meningitidis serogroup C infection. Patients with conditions that can raise PCT-Q levels were excluded (chronic illness, recent surgery or recent multiple trauma). All patients were monitored on admission and were treated according to their meningococcal infection protocol (antibiotics, rehydration, inotropic drugs and mechanical ventilation if the patient presented with shock or respiratory failure).</td><td>
* P <0.05 (McNemar test significance >=10 ng/ml vs. <10 ng/ml)
** P <0.001 (McNemar test significance >=10 ng/ml vs. <10 ng/ml)

ROC curve analysis showed that PCT-Q and NC, but not CRP, were significantly associated with shock, MODS and death . The cut-offs selected were <1000 mm^3 for NC and <=8 mg/dl for CRP. PCT-Q had a higher sensitivity for shock (P <0.01), MODS (P <0.001) and death (P <0.001) than absolute NC, which had a higher specificity than PCT-Q for shock (P <0.001), MODS (P <0.001) and death (P <0.001).

Table: Area under ROC curves of PCT-Q test >=10 ng/ml, absolute NC <1000 mm^3 and CRP <= mg/l as a predictor of poor outcome in 65 children with meningococcal infection. (AUC area under the curve)
<table>
<tr><td></td><td>AUC (SE) [a]</td><td>95% CI AUC</td></tr>
<tr><td>Death</td><td></td><td></td></tr>
<tr><td>PCT-Q (ng/ml)</td><td>0.70*** (0.07)</td><td>0.55–0.84</td></tr>
<tr><td>NC (mm^3)</td><td>0.76*(0.08)</td><td>0.62–0.91</td></tr>
<tr><td>CRP (mg/ml)</td><td>0.62 (0.09)</td><td>0.44–0.79</td></tr>
<tr><td>MODS</td><td></td><td></td></tr>
<tr><td>PCT-Q (ng/ml)</td><td>0.73* (0.06)</td><td>0.62–0.85</td></tr>
<tr><td>NC (mm^3)</td><td>0.86** (0.05)</td><td>0.77–0.95</td></tr>
<tr><td>CRP (mg/ml)</td><td>0.63 (0.08)</td><td>0.48–0.78</td></tr>
<tr><td>Shock</td><td></td><td></td></tr>
<tr><td>PCT-Q (ng/ml)</td><td>0.64* (0.07)</td><td>0.50–0.77</td></tr>
<tr><td>NC (mm^3)</td><td>0.81** (0.06)</td><td>0.69–0.92</td></tr>
<tr><td>CRP (mg/ml)</td><td>0.59 (0.07)</td><td>0.45–0.73</td></tr>
</table>
</td></tr>
</table>

Citation/ EL	Methodology	Effect size

[a]AUC significance (null hypothesis AUC = 0.50)

* *P* <0.05, ** *P* =0.001, *** *P* =0.06

Table Indices of PCT-Q >10 ng/ml, absolute NC <1000 mm^3 and CRP <=8 mg/ml as a predictor of poor outcome in 65 children with meningococcal infection. The data are given in % and CI 95% (95% confidence interval). (*NPV:* negative predictive values, *PPV:* positive predictive values, RR: relative risk, PLR: positive likelihood ratio, NLR: negative likelihood ratio)

	Cases (*n*)	Sensitivity	Specificity	PPV	NPV	RR	PLR	NLR	OR
Death									
PCT-Q >=10 ng/ml	9 (9)	100.0 (62.9–100.0)	39.3 (26.8–53.3)	20.9 (10.6–36.5)	100.0 (81.5–100.00)	--	1.65 (1.3–2.0)	0.0 (0.0–0.9)	165
NC <1.000 mm^3	2 (8)	25.0 (4.5–64.4)	92.8 (81.6–97.6)	33.3 (6.0–75.9)	89.5 (77.8–95.7)	3.17	3.4 (0.8–15.8)	0.8 (0.5–1.2)	4.25
CRP>=8 mg/ml	6 (9)	66.7 (30.9–91.0)	55.4 (41.6–68.2)	19.4 (8.1–38.1)	91.2 (75.2–97.7)	2.2	1.5 (0.9–2.6)	0.6 (0.2–1.6)	2.5
MODS									
PCT-Q >=10 ng/ml	18 (18)	100.0 (78.1–100.0)	46.8 (32.4–61.8)	41.9 (27.4–57.8)	100.0 (81.5–100.0)	--	1.9 (1.4–2.5)	0.0 (0.0–0.8)	190
NC <1.000 mm^3	5 (17)	29.4 (11.4–56.0)	97.8 (87.0–99.9)	83.3 (36.5–99.1)	78.9 (65.8–88.2)	3.95	13.5 (1.7–107.7)	0.7 (0.5–1.0)	19.3
CRP >= 8 mg/ml	12 (18)	66.7 (41.1–85.6)	59.6 (44.3–73.3)	38.7 (22.4–57.7)	82.4 (64.8–92.6)	2.20	1.7 (1.0–2.7)	0.6 (0.3–1.1)	2.8
Shock									
PCT-Q >= 10 ng/ml	26 (33)	78.8 (60.6–90.4)	46.9 (29.5–65.0)	60.5 (44.5–74.6)	68.2 (45.1–85.3)	1.90	1.5 (1.0–2.2)	0.45 (0.2–1.0)	3.3

<table>
<tr><th>Citation/ EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>NC <1.000 mm^3</td><td>6 (31)</td><td>19.4 (8.1–38.1)</td><td>100.0 (86.7–100.0)</td><td>100.0 (51.7–100.0)</td><td>56.1 (42.4–69.0)</td><td>2.28</td><td>6.2 (0.2–5.7)</td><td>0.8 (0.7–1.0)</td><td>7.75</td></tr>
<tr><td>CRP >= 8 mg/ml</td><td>20 (33)</td><td>60.7 (42.2–76.6)</td><td>65.6 (46.8–80.8)</td><td>64.6 (45.4–80.2)</td><td>61.8 (43.6–77.3)</td><td>1.69</td><td>1.8 (1.0–3.1)</td><td>0.6 (0.4–1.0)</td><td>3</td></tr>
</table>
</td></tr>
<tr><td>Korppi[269]

<u>Study type:</u> prospective cohort study.

EL: II</td><td><u>Country:</u>

Finland

<u>Aim:</u>

To examine whether PCT can be applied for the discrimination between bacterial and especially pneumococcal pneumonia and viral aetiology of pneumonia.

Setting, inclusion/ exclusion:

In the course of a prospective study in 1981–1982, 195 children were treated for presumed pneumonia in the Dept of Paediatrics, Kuopio University Hospital, Finland. The diagnosis of pneumonia, based on pulmonary infiltrations on chest radiographs evaluated by two radiologists, was confirmed in 161 cases. In 1999, there were 132 acute serum samples (82%) available for PCT measurements, and these cases form the material of the present study. Twenty-seven per cent of the patients were infants <12</td><td>Pneumococcal aetiology was studied by antigen assays in acute serum and urine, by antibody assays to capsular C-polysaccharide (C-PS), to type-specific capsular polysaccharides (CPS) and to pneumolysin (PNL) in paired sera, and by immune complex assays measuring circulating C-PS, CPS and PNL specific complexes in acute and convalescent sera. Among the 132 patients of the present study, the antigen assays were positive in six cases, antibody assays in 14 cases and immune complex assays in 21 cases. Based on combined serological data, S. pneumoniae aetiology was indicated in 41 cases (32%). Viral aetiology was studied by antibody assays in paired sera and antigen assays in nasopharyngeal aspirates for respiratory viruses, including RSV, parainfluenza 1, 2 and 3, influenza A and B, and adenoviruses. A viral infection was diagnosed in 38 cases; among them, RSV was identified in 30 cases.

The association between the type of infiltration, that is alveolar or interstitial, and serum PCT concentrations was studied in a total of 132 children with radiologically verified pneumonia. The median PCT was 0.45 ng/mL (25th–75th percentile 0.22–1.20) in children with alveolar pneumonia and 0.28 ng/mL (0.11–0.71) with interstitial pneumonia (p=0.067). Serum PCT values were significantly lower in children <2 yrs old than in older children; the medians (25th–75th percentile) were 0.24 ng/mL (0.11–0.62) and 0.49 ng/mL (0.13–1.15), respectively (p=0.02). The medians were 0.23 ng/mL and 0.25 ng/mL before 12 months and between 13 and 23 months of age, respectively. The association between the type of infiltration and PCT values was analysed also by the multiple linear regression model, adjusted for age, and the association remained nonsignificant (data not shown). A low PCT <0.5 ng/mL was present in 79 children (60%). The respective figure for high PCT >2.0 ng/mL was 11 (8%); nine (82%) children were >2 yrs old (p<0.05 versus younger children).

Table : Serum procalcitonin (PCT) in 132 children with pneumonia in relation to the radiological type of infiltration

<table>
<tr><th></th><th colspan="2">Type of pneumonia</th></tr>
<tr><th>Serum PCT</th><th>Alveolar</th><th>Interstitial</th></tr>
</table>
</td></tr>
</table>

Citation/ EL	Methodology	Effect size
	months and 53% were <24 months of age. The mean age was 3.0 yrs, and 64% were males. The type of pneumonia was alveolar in 46 cases and interstitial in 86 cases.	

ng/mL	-value[a]	
Subjects	46	86
Median 25th–75th percentile[a]	0.45 (0.22–1.2)	0.28 (0.11–0.71)
<0.5	25 (54)	54 (63)
0.5–1.0	7 (15)	19 (22)
1.0–2.0	10 (22)	6 (7)
>2.0	4 (9)	7 (8)

Data presented as n (%) or median (25th–75th percentile). [a]: p%0.067, determined using the Wilcoxon rank-sum test.

The association between the aetiology of infection and PCT values were studied in the 119 children with viral, pneumococcal or unknown aetiology of pneumonia. No difference was seen between these groups, and mixed infections did not differ from single PNC or viral infections. Adjustment for age by the multiple regression analysis did not influence the results (data not shown). Serum PCT was >1.0 ng/mL in 40% of PNC cases, as compared to 12–15% of viral or mixed cases, respectively (p<0.05). Likewise, the median PCT was 0.81 ng/mL (25th–75th percentile 0.17–1.57) in children with single PNC pneumonia and only 0.48 ng/mL (0.19–0.69) in those with single viral pneumonia; the difference was not statistically significant (p=0.11). The PCT values varied from immeasurable to 6.4 ng/mL, and the variation was wide within all aetiological groups.

Table : Serum procalcitonin (PCT) in 119 children with pneumonia in relation to the aetiology of infection

Aetiological group of infection				
Serum PCT ng/mL	PNC	Mixed	Viral	Unknown

Citation/ EL	Methodology	Effect size

Subjects	25	13	17	64
Median 25th–75th percentile[a]	0.81 (0.17–1.57)	0.50 (0.33–0.62)	0.48 (0.19–0.69)	0.26 (0.10–0.79)
<0.5	11 (42)	6 (46)	12 (71)	41 (64)
0.5–1.0	4	7	3	14
1.0–2.0	7	2	1	4
>2.0	3	0	1	7

Data presented as absolute values or n (%). The 13 cases with *Haemophilus influenzae*, *Branhamella catarrhalis*, *Mycoplasma. pneumoniae* and *Chlamydia* sp aetiology are excluded. PNC: pneumococcal; [a]: p%0.11, determined using Kruskal-Wallis test.

The PCT values of 0.5 ng/mL, 1.0 ng/mL and 2.0 ng/mL were tested as screening limits between PNC and viral pneumonia. In this analysis, the cases with PNC aetiology, whether single or mixed, were combined to the group of PNC pneumonia, and single viral cases formed the viral pneumonia group. The highest sensitivity was 55% at the 0.5 ng/mL cut-off level, being of course, lower at higher levels. The highest specificity 88% was reached at the level of 1.0 ng/mL. At best, the likelihood ratio for the positive result was 2.6 and for the negative result 0.6, being far from optimal (>10 for LR+ and <0.1 for LR–).

Table : Diagnostic parameters for serum procalcitonin in differentiating pneumococcal (PNC) from viral pneumonia.

Diagnostic parameters					
Cut-off limit	PNC present	Sensitivity %	Specificity %	LR+ %	LR– %
>0.5 ng/mL	21	55	71	1.9	0.6

Citation/ EL	Methodology	Effect size

1.0 ng/mL	12	32	88	2.6	0.8
>2.0 ng/mL	3	8	95	1.6	1.0

LR+: likelihood ratio for the positive result; LR–: likelihood ratio for the negative result; Pneumococcal pneumonia consisted of 26 single and 15 mixed viral PNC cases; viral pneumonia consisted of 17 single viral cases.

A significant association was seen between serum PCT and CRP concentrations, but not between PCT and WBC or ESR results. When PCT was <0.5 ng/mL, CRP was under 60 ng/mL in 86% of the cases. The agreement between the higher values was less pronounced.

Table : Association between serum procalcitonin and other nonspecific inflammatory parameters in 119 pneumonia patients with pneumococcal, viral or unknown aetiology.

	Serum procalcitonin concentration (ng/mL)			
	<0.5	0.5–1.0	>1.0 ng/mL	p-value
Subjects	70	24	25	
CRP>60 ng/mL	6	8	14	<0.001
CRP<60 ng/mL	64	16	11	
WBC>15x10^9/L	23	7	14	NS
WBC<15x10^9/L	47	17	11	
ESR>30mm/h	27	10	12	NS
ESR<30mm/h	43	14	13	

<table>
<tr><th>Citation/ EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td></td><td>: determined using Chi-squared test. CRP: C-reactive protein; WBC: white blood cell; ESR: erythrocyte sedimentation rates.</td></tr>
<tr><td>Moulin[174]

<u>Study type:</u> prospective cohort study

EL: II</td><td><u>Country:</u>

France

<u>Aim:</u>

To assess the sensitivity, specificity, and predictive value of procalcitonin (PCT) in differentiating bacterial and viral causes of pneumonia.

<u>Setting, inclusion/ exclusion:</u>

Of 88 patients (aged 2 months to 13 years) admitted to hospital for severe community acquired febrile pneumonia between 1 January 1996 and 1 November 1999, pathogens were identified in 72. They included only those children who were immunocompetent, who had no chronic disease, pulmonary or otherwise, and who had not received antibiotics in the 10 days before admission. The remaining children accounted for 60% of children examined in the emergency department for pneumonia in this period. The other patients were not included because they had already been treated, they were not</td><td>A total of 88 patients were admitted for community acquired pneumonia; 16 had no pathogen identified and were not included in the study. Of the 72 patients studied, 10 (mean age 1.9 years; range 0.4-5 years) had blood cultures positive for Streptococcus pneumoniae and 15 (mean age 3.9 years; range 0.5-14 years) had bacterial pneumonia diagnosed on the basis of bacteriological and cytological criteria: more than 25 polymorphonuclear cells and less than 10 epithelial cells, and cultures containing a single or a predominant microorganism, with more than 10^6 CFU/ml (S pneumoniae in 14 and Haemophilus influenzae b in one). All these patients tested negative in serological tests for viruses, Mycoplasma, and Chlamydia, and became afebrile within 48 hours of treatment with amoxicillin (or ceftriaxone for the youngest patients). In 37 cases, viral pneumonia was diagnosed by immunofluorescence techniques, viral cultures, or serological tests. In 29 patients (mean age 1.7 years; range 0.5-7 years) viruses were apparently the sole cause of pneumonia (respiratory syncytial virus in eight, adenovirus in seven, influenza A virus in seven, and parainfluenza 2 or 3 viruses in seven) because bacteria were not detected in blood cultures and were not present in large numbers in the sputum. In eight other patients (mean age 1.3 years; range 0.5-5 years), a virus was identified by serological tests, immunofluorescence, or virus culture, and there were more than 25 polymorphonuclear cells and less than 10 epithelial cells in sputum, and cultures containing a single or predominant microorganism, with more than 10^6 CFU/ml were obtained (S pneumoniae in six, Haemophilus influenzae b in two). These eight patients were considered to have mixed bacterial and viral infections. Ten patients (mean age 6.2 years; range 3-10 years) had positive serological tests (presence of IgM and/or quadrupling of IgG concentrations) for Mycoplasma pneumoniae.

At admission, all patients had fever (temperature above 38 °C), and were admitted to the hospital based on clinical examinations by doctors in charge of the emergency department. Hypoxaemia requiring oxygen supplementation on admission was diagnosed in eight of the 10 patients with positive blood culture, in 13 of the 32 patients with bacterial pneumonia and negative blood culture, and in 19 of the 29 patients with viral pneumonia. Chest x ray showed notable alveolar infiltration in 64 of the 72 patients: total lobar infiltration in 31, and minor alveolar infiltration in 33. Interstitial infiltration was found in the eight others (virus in five, mycoplasma in two, bacterial pneumonia in one).

Table : Values at hospital admission for the different groups of patients with pneumonia

<table>
<tr><th></th><th>PCT (µg/l)</th><th>CRP (mg/l)</th><th>IL-6 (pg/ml)</th><th>WBC (×10^9/l)</th></tr>
<tr><td>Bacterial pneumonia</td><td></td><td></td><td></td><td></td></tr>
<tr><td>S pneumoniae</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Blood culture (n = 10)</td><td>20.5 (2.3-90.6)</td><td>214.4 (39-400)</td><td>796 (95-1779)</td><td>20.2 (6.7-45)</td></tr>
</table>
</td></tr>
</table>

Citation/ EL	Methodology	Effect size

subsequently admitted to hospital, or blood was not collected for PCT determination.

On admission, all patients had a body temperature above 38 °C and a chest *x* ray picture indicative of pneumonia, as analysed by an independent radiologist. The patients were all admitted as emergency cases on the basis of their clinical condition, assessed by the doctor in charge of the emergency department of the hospital who did not know the results of PCT determination.

Sputum (1 pt *H influenzae* b) (n = 15)	10.0 (0.6-21)	197 (15-400)	529 (11-1680)	23.9 (10.4-42.5)
M pneumoniae (n = 10)	1.53 (0.3-4.7)	103.1 (10-348)	156.7 (45-360)	13.8 (6.9-26.5)
Virus + bacterial superinfection (n = 8)	2.68 (0.6-7.6)	95.2 (16-249)	381.6 (10-1400)	13.8 (6.1-35.1)
Viral pneumonia (n = 29)	0.63 (0.01-4.38)	39.1 (1-169)	122 (15-580)	10.3 (2.8-22.5)

Table Validity coefficients of tests for selected cut off points in the discrimination between bacterial (including mycoplasma and bacterial + viral co-infections) and viral pneumonia

	Bacterial	Viral	Sensitivity	Specificity	PPV	NPV	RR*
PCT > 0.5 µg/l	41/43	10/29	95%	60%	80.3%	88.4%	6.92
PCT > 1 µg/l	37/43	4/29	86%	87.5%	90.2%	80%	4.51
PCT > 2 µg/l	27/43	1/29	62.7%	96%	96.4%	60%	2.41
CRP > 20 mg/l	38/43	15/29	88.4%	40%	71.6%	66.6%	2.14
CRP > 60 mg/l	30/43	7/29	69.8%	52%	81.1%	58.1%	1.94
IL-6 > 100 pg/ml	12/20	2/12	66%	83%	85.7%	55.5%	1.93
WBC > 15 000 ($\times 10^6$/l)	28/43	6/29	65.1%	79.3%	82.3%	60.5%	2.08
*: RR: relative risk.							

CRP concentrations were greater than 20 mg/l in all 10 patients with positive blood cultures (>40 mg/l in nine and >60 mg/l in eight). In cases of isolated viral infection, CRP was greater than 20 mg/l in 15 of the 29 patients and above 60 mg/l in seven. The highest CRP concentrations in viral infections were found in patients infected with adenovirus. Considering all bacterial infections, positive blood cultures, contributory bacterial samples, secondary bacterial infections in cases of viral pneumonia, positive serological tests for anti-*Mycoplasma* antibodies, and isolated viral infections, we found that a CRP concentration of 20 mg/l had a sensitivity very similar to that of a PCT concentration of 1 µg/l (88.4% *v* 86%), but a much lower specificity (40% *v* 87.5%) for discriminating between bacterial and viral infections. White blood cell count above 15 000/ml discriminated poorly between

<table>
<tr><th>Citation/ EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td></td><td>bacterial and viral infections. PCT, CRP, WBC, and IL-6 values differed significantly (t test, p < 0.005) between cases of bacterial and viral pneumonia. However, PCT is a better marker of invasive pneumococcal infection than CRP. Mean PCT concentration was 20.5 ng/ml in patients with positive blood cultures and 7.5 ng/ml in patients with bacterial pneumonia and negative blood cultures (p < 0.01); mean CRP concentration was 214 and 161 mg/l respectively (non-significant) in these two groups.

In all cases, PCT concentration differentiated viral and bacterial infections more effectively than CRP, IL-6, or WBC counts. The area under the ROC curve was 0.93 for PCT (95% confidence interval (CI) 0.85 to 0.97), 0.84 for CRP (95% CI 0.73 to 0.91), and 0.64 for IL-6 (95% CI 0.45 to 0.80). The areas under the ROC curves were compared: p < 0.04 for PCT v CRP, and p < 0.003 for PCT v IL-6.</td></tr>
<tr><td>Gendrel[270]

<u>Study type</u>: prospective cohort study

EL: II</td><td><u>Country:</u>

France

<u>Aim:</u>

To evaluate PCT levels to discriminate between bacterial and viral meningitis in young children and infants.

<u>Setting, inclusion/ exclusion:</u>

They included 59 consecutive children hospitalised for meningitis during 1 January 1994 to 31 December 1995 who had not received antibiotic treatment. Patients (neonates were excluded) were included if the initial blood sample collected for routine analyses was available. During this period, initial blood samples from two children with bacterial meningitis and 24 with aseptic meningitis (for which viral origins were clearly demonstrated) were not available, and they were excluded.</td><td>Eighteen of 59 patients, aged from 3 months to 13 years (mean, 3.6 yr), were hospitalised for acute bacterial meningitis. Forty-one patients (mean age 2.6 year, range 1mo to 10 yrs) had acute viral meningitis. All patients in this group had symptoms of meningitis, CSF leukocyte counts of > 20/µL, and negative bacterial cultures; none had bacterial antigen detected in CSF.

Viral cultures were positive in 7/41 cases; enterovirus was detected in four, adenovirus, in two; and varicella-zoster virus, in one. Two patients had viral meningitis during the episode of mumps. Reverse transcriptase-PCR revealed the presence of enterovirus RNA in CSF for 17 patients.

The difference of the mean values for CSF leukocyte counts, CSF protein levels, CRP levels and PCT levels were statistically significant for any of the four tests.

Two patients with bacterial meningitis and five with viral meningitis had overlapping CRP values of 20-50 mg/L.

The PCT levels were discriminate in all cases. The mean PCT level on admission in patients with acute bacterial meningitis was 54.5µg/L, and the lower level was 4.8µg/L, while the higher level in patients with viral meningitis was 1.7 µg/L (mean = 0.32µg/L).

Table : Levels of CSF leukocyte counts, CSF protein, CRP and PCT in children with bacterial and viral meningitis.
<table>
<tr><td>Diagnosis</td><td>CSF cells (/µL)</td><td>CSF protein (g/L)</td><td>CRP (mg/L)</td><td>PCT (µg/ L)</td></tr>
<tr><td>Bacterial meningitis</td><td>5,156+-4,336</td><td>2.3+-1.2</td><td>144+-69</td><td>54.5+-35.1</td></tr>
<tr><td>(n=18)</td><td>(250-17,500)</td><td>(0.4-1.47)</td><td>(28-311)</td><td>(4.8-110)</td></tr>
<tr><td>Viral meningitis</td><td>391+-648</td><td>0.62+-0.47</td><td>14.8+-14.1</td><td>0.32+-0.35</td></tr>
<tr><td>(n=41)</td><td>(20-3,200)*</td><td>(0.12-2.72)*</td><td>(0-48)*</td><td>(0-17)**</td></tr>
<tr><td colspan="5">Note: data are mean+- SD (range).* p<0.001; **: p<0.0001.</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Citation/ EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td></td><td>With a PCT level of > 5µg/L, the sensitivity for diagnosis of bacterial meningitis was 94% and 100% of specificity.

Nineteen patients with viral meningitis received antibiotic as presumptive treatment. Initial PCT levels ranged from 0.1-0.65µg/L and these were similar to those children with untreated viral meningitis (statistics not provided).

PCT levels were measured during treatment on eight patients with bacterial meningitis. In all cases, a marked decrease was observed.

All patients had PCT <1µg/L at recovery. PCT levels were measured in eight patients with viral meningitis on the second and third days. These levels always remained <1µg/L. PCT levels in blood and CSF samples collected at the same time were determined for six patients with bacterial meningitis and 12 with viral meningitis. No PCT was found in the CSF samples.</td></tr>
<tr><td>Gendrel[271]

Study type: prospective cohort

EL: II

May be partial duplication of publication with study 4151 (overlapping of population).</td><td>Country:

France

Aim

To test the hypothesis that if PCT is the best marker in children with fever admitted to hospital as emergency cases.

Setting, inclusion/ exclusion:

From January 1994 to December 1996, 74 infants or children (not defined) hospitalised for meningitis were included if a blood sample from initial collection was available after all the routine biological test. 23 children, aged from 3 months to 13 years (mean age: 3.2 yr), were hospitalised for acute bacterial meningitis (BM). 41 patients (mean age 2.2 yr, range 1 month to 10 yr) were diagnosed with acute viral meningitis (VM). All patients in this</td><td>The differences of the mean of the five tests (see table below) were highly significant. However, a wide range with over lapping was found in all markers but PCT.

Table : Levels of CSF leukocyte counts, CSF protein, CRP and PCT in children with bacterial and viral meningitis.
<table>
<tr><td>Diagnosis</td><td>CSF protein (g/L)</td><td>CSF cells (/ml)</td><td>CRP (mg/L)</td><td>IL6(pg/ml)</td><td>PCT (µg/ L)</td></tr>
<tr><td>Viral meningitis</td><td>0.57</td><td>345</td><td>13.9</td><td>82.5</td><td>0.32</td></tr>
<tr><td>(n=51)</td><td>(20.1-2.7)</td><td>(10-3200)</td><td>(1-48)</td><td>(0-450)</td><td>(0-1.7)</td></tr>
<tr><td>Bacterial meningitis</td><td>2.2*</td><td>4710*</td><td>143.3*</td><td>1340.9*</td><td>60.9**</td></tr>
<tr><td>(n=23)</td><td>(0.4-4.7)</td><td>(10-17500)</td><td>(28-350)</td><td>78-3200)</td><td>(4.8-335)</td></tr>
<tr><td colspan="6">Note: data are mean+- SD (range).* p<0.001; **: p<0.0001.</td></tr>
</table>
Table :Individual values of PCT, CRP and IL6 in meningitis.
<table>
<tr><td colspan="4">Viral meningitis</td></tr>
<tr><td>Age</td><td>PCT (µg/ L)</td><td>CRP (mg/L)</td><td>IL6 (pg/ml)</td></tr>
<tr><td>6m</td><td>0</td><td>42</td><td>0</td></tr>
</table></td></tr>
</table>

Citation/ EL	Methodology	Effect size			
	group had symptoms of meningitis. Viral cultures were positive in 7/41 cases; enterovirus was detected in four, adenovirus, in two; and varicella-zoster virus, in one. Two patients had viral meningitis during the episode of mumps. Reverse transcriptase-PCR revealed the presence of enterovirus RNA in CSF for 17 patients.	10m	0	<8	0
		18m	0	<8	0
		5y	0.15	<8	1.2
		9m	0.1	<8	19
		10m	0.55	12	19
		4m	0.19	<8	20
		4m	0.01	9	23
		2m	0.32	<8	25
		10m	0.25	25	37
		7y	0.17	25	56
		2y	0.1	10	97
		3m	0.1	8	135
		9m	0.15	<8	135
		2m	0.15	10	150
		2y	0.2	<8	180
		5y	0.1	<8	220
		2m	0.73	<8	220
		6y	0	55	450
		Bacterial meningitis			
		Age (bacteria if available)	PCT (µg/ L)	CRP (mg/L)	IL6 (pg/ml)
		N. meningitis/ 4 mo	76.6	215	2000
		2y	16	98	990
		9m	335	118	3200
		10 m	6.48	78	2700

<table>
<tr><th>Citation/ EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>S. pneumoniae/ 6 m</td><td>4.8</td><td>180</td><td>363</td></tr>
<tr><td>5m</td><td>6.4</td><td>143</td><td>2095</td></tr>
<tr><td>3m</td><td>8.3</td><td>100</td><td>1640</td></tr>
<tr><td>H. influenzae b/ 2y</td><td>65.9</td><td>351</td><td>78</td></tr>
</table>

PCT was measured during treatment in patients with BM. A decrease was observed and values < 1µg/ L were reached at recovery. In 12 patients with VM measured in the 2nd and 3rd days, PCT remains always <1µg/ L.</td></tr>
<tr><td>Gendrel[271]

(study 2)

<u>Study type:</u> prospective cohort

EL: II</td><td><u>Country:</u>

France

<u>Aim:</u>

To assess the efficiency of PCT at admission in children for the diagnosis of bacterial vs. viral infections and determine a cut-off value.

<u>Setting, inclusion/ exclusion:</u>

PCT was prospectively measured, from 1996-1997, on samples collected in ER in the sera of 450 children (1m-12 yr) examined for fever >38.5C without previous antibiotic treatment. Data were analysed only in patients with a proved aetiology of infection.</td><td>Final diagnosis with assessed diagnosis bacterial or viral infection was:

Severe bacterial infection: n=43; 18 meningitis, 20 septicaemia, 6 pneumococcal pneumonia.

Localised bacterial infection: n=39 (negative blood culture); 15 UTI, 10 ENT infections.

Viral infection: n=161; 55 enterovirus, 38 rotavirus, 40 RSV, 10 EBV.

PCT was always low in 6 feverish patients hospitalised at same time with inflammatory disease (arthritis, Crohn disease).

Mean PCT was 36.8µg/ L in 43 children with bacterial invasive infection (meningitis, septicaemia and pneumonia). Initial PCY was >1.5µg/ L in 41/43 in this group (sensitivity:95.3%) and in 24/39 in children with localised bacterial infection (sensitivity: 61.5%). Mean PCT in the group with localised bacterial infection was 3.1µg/ L (range 0.1-12µg/ L) and 0.4µg/ L in viral infections.

In 5/161 children with a proved viral infections had PCT>1.5µg/ L (specificity:97%). In bacterial non invasive infections, PCT is a marker comparable to CRP but superior to IL6 which was found >100pg/ml in 27 of patients in this group.

In this study, PCT of 1.5µg/ L had better sensitivity and specificity than CRP and IL6.</td></tr>
<tr><td>Korppi[272]

<u>Study design:</u>

Prospective cohort</td><td><u>Country</u>

Finland

<u>Aim:</u>

To examine whether PCT can be used to differentiate between viral</td><td>The median PCT concentrations were 0.47, 0.46 and 0.35 in children < 5yr, 1-5 yr and > 5yr respectively (p=0.0041, Kruskal-Wallis test). The PCT level tended to be lower in children <1yr than in 1-5 yr (0.42 vs. 0.51 ng/ml, p=0.066 sum rank test).

Serum PCT was not related to severity of illness (outpatients vs. inpatients; sum rank test p=0.77); and remained insignificant using linear regression model adjusted for age (details not provided).</td></tr>
</table>

<table>
<tr><th>Citation/ EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td>study

EL: II</td><td>and bacterial aetiology of community acquired pneumonia (CPA) in the primary healthcare setting.

<u>Setting, inclusion/ exclusion:</u>

During 1981-1982 (month of the year not stated), all cases of pneumonia were prospectively collected in the area of east Finland in a previously constructed sampling frame. In all, 201 CPA patients <= 15 yr were identified. The diagnosis was verified radiologically. In 1999, there were 190 serum samples (94.5%) available for PCT measurements. Half of those were < 5years, 24.7% were between 5-9 yr and 25.3% were >=10 yr. 132 patients (69.5%) were treated as outpatients, and 58 as inpatients.

The 57 pneumococcal infections, including 20 single and 37 mixed infections, were considered as having S pneumoniae pneumonia.</td><td>Table : Aetiology and serum PCT in 190 children with pneumonia.

<table>
<tr><td>Serum PCT</td><td>Pneumococcal (n=57)</td><td>Mycoplasma Chlamydia (n=48)</td><td>Viral (n=29)</td><td>Unknown (n=56)</td><td>P (Kruskal-Wallis test)</td></tr>
<tr><td>Median</td><td>0.47</td><td>0.39</td><td>0.49</td><td>0.44</td><td>0.083</td></tr>
<tr><td>25th-75th percentile</td><td>0.27-0.79</td><td>0.27-0.79</td><td>0.32-0.74</td><td>0.36-0.66</td><td></td></tr>
<tr><td></td><td>N(%)</td><td>N(%)</td><td>N(%)</td><td>N(%)</td><td></td></tr>
<tr><td><0.5 ng/ml</td><td>31(54)</td><td>33 (69)</td><td>15 (52)</td><td>34 (61)</td><td></td></tr>
<tr><td>0.5-1.0 ng/ml</td><td>15 (26)</td><td>11 (23)</td><td>11 (38)</td><td>17 (30)</td><td></td></tr>
<tr><td>1.0-2.0 ng/ml</td><td>10 (18)</td><td>3(6)</td><td>2 (7)</td><td>4 (7)</td><td></td></tr>
<tr><td>>2.0 ng/ml</td><td>1 (2)</td><td>1(2)</td><td>1(3)</td><td>1 (2)</td><td></td></tr>
</table>
There is no statistical difference between different aetiologies and they remained insignificant using linear regression model adjusted for age (details not provided).

PCT was > 1.0 ng/mL in 19.3 of pneumococcal cases, as compared to 8.3-10.3% of Mycoplasma Chlamydia cases and viral cases, respectively (p>0.25 for both, chi square test).

Table: PCT concentration in differentiating pneumococcal from viral pneumonia; and Mycoplasma-Chlamydia from viral pneumonia.

<table>
<tr><td>Cut-off limit</td><td>S. pneumoniae present (n=57)</td><td>Sensitivity %</td><td>Specificity%</td><td>PPV%</td></tr>
<tr><td>>0.5 ng/ml (n=40)</td><td>26</td><td>46</td><td>52</td><td>65</td></tr>
<tr><td>>1.0 ng/ml (n=14)</td><td>11</td><td>24</td><td>90</td><td>79</td></tr>
<tr><td>Cut-off limit</td><td>Mycoplasma or Chlamydia present (n=48)</td><td>Sensitivity %</td><td>Specificity%</td><td>PPV%</td></tr>
<tr><td>>0.5 ng/ml (n=29)</td><td>15</td><td>31</td><td>51</td><td>52</td></tr>
<tr><td>>1.0 ng/ml (n=7)</td><td>4</td><td>8</td><td>90</td><td>57</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/ EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td></td><td>*: NPVs not reported.

The PCT of 0.5 and 1.0ng/ml were tested as screening limits between pneumococcal and viral pneumonia. The likelihood ratio (LR) was low (<1.0) at the 0.5 ng/ml level, and LR:2.4 at the level of 1.0ng/ml</td></tr>
<tr><td>Ballot[273]

<u>Study design:</u>
Prospective cohort study

EL: II</td><td><u>Country</u>
South Africa
<u>Aim:</u>
To evaluate the role of PCT as a single early marker of neonatal sepsis.
<u>Setting, inclusion/ exclusion:</u>
This study was done in the neonatal unit in Johannesburg hospital between April to August 2002. All neonates undergoing sepsis evaluation were eligible. Sepsis evolution were done for several reasons including maternal risk of sepsis, and signs and symptoms of neonatal sepsis (e.g. temperature instability, lethargy, feeding intolerance, seizure, ongoing respiratory distress, irritability, blood glucose abnormality, hypotension, poor perfusion, acidosis).</td><td>Babies were categorised to the followings:
<u>No infection:</u> negative blood cultures with normal CRP1 and CRP2, platelet count and WCC.
<u>Possible infection:</u> negative blood cultures with abnormal CRP1 and CRP2; or combination of at least two of the followings: abnormal CRP1 and CRP2, platelet count and WCC.
<u>Definite infection:</u> positive blood cultures with abnormal CRP1 and CRP2; or combination of at least two of the followings: abnormal CRP1 and CRP2, platelet count and WCC.

216 patients were recruited and 28 were excluded because of incomplete data, a further 5 babies were excluded due to contamination. And there were 183 babies in the final analysis. The mean birthweight is 1996g (SD:893) and gestational age 34.6 wk (SD:4.3). The majority (167/183: 91%) were evaluated within the first 72 hr of life. There were 13 babies were classified as definite infection, 52 with possible infection and 118 with no infection. PCT correlated with CRP1 (r=0.404,p<0.001) and CRP2 (r=0.343, p<0.001).
logistic regression showed that PCT alone predicted 72.5% of any infection an and 89.2% of definite infection, and after the adjustment of gestational age and platelet count, the prediction became 79.1% and 90.4% respectively.
Table : predictive values for PCT>0.5ng/ ml
<table>
<tr><th>Infection category</th><th>Sensitivity %</th><th>Specificity %</th><th>PPV %</th><th>NPV %</th><th>RR</th></tr>
<tr><td>None vs. any</td><td>78</td><td>50</td><td>46</td><td>80</td><td>2.3</td></tr>
<tr><td>None vs. definite</td><td>77</td><td>50</td><td>14</td><td>95</td><td>2.8</td></tr>
</table>
</td></tr>
<tr><td>Wafula[273]

<u>Study type:</u></td><td><u>Country:</u>
Nairobi
<u>Aim</u>:
To assess the diagnostic value of</td><td>One hundred and fifty patients were studied with male to female ratio of 1:1. 24% were < 12 mo. Of the 150 study patients, 90 (60%) had radiological evidence pneumonia while the rest had normal radiographs .Resp Rate (RR)>50/ min, nasal flaring and chest indrawing were the most sensitive and specific predictors.</td></tr>
</table>

<table>
<tr><th>Citation/ EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td>(Prospective?) Cohort study

EL:II</td><td>commonly used signs for severe acute respiratory infection (ARI).

<u>Setting, inclusion/ exclusion:</u>

Between July 1985 to December 1985, children aged 5 months to 5 years presenting at the Paediatric observation ward or the paediatric Filter clinic of Kenyatta Hospital with histories of cough of < 2 weeks were recruited. The recruitment was carried out during normal working hours for convenience. Children with the following were excluded: those already on medication, in congestive heart failure, moderate to severe dehydration, with known metabolic disorder and obvious chest deformities.</td><td>Table : frequency of clinical features
<table><tr><th>Clinical feature</th><th>Sensitivity %</th><th>Specificity %</th><th>PPV %</th><th>NPV %</th><th>Risk ratio</th></tr><tr><td>Hx*of fast breathing</td><td>81</td><td>65</td><td>78</td><td>70</td><td>2.60</td></tr><tr><td>Hx*of poor feeding</td><td>93</td><td>28</td><td>66</td><td>74</td><td>2.54</td></tr><tr><td>Hx*of fever (>37.5^{O}C)</td><td>92</td><td>28</td><td>66</td><td>71</td><td>2.27</td></tr><tr><td>HR >140/ min</td><td>92</td><td>47</td><td>72</td><td>80</td><td>3.6</td></tr><tr><td>RR>40/min</td><td>96</td><td>42</td><td>71</td><td>86</td><td>5.07</td></tr><tr><td>RR>50/min</td><td>96</td><td>42</td><td>71</td><td>86</td><td>5.07</td></tr><tr><td>Nasal flaring</td><td>79</td><td>72</td><td>81</td><td>69</td><td>2.61</td></tr><tr><td>Chest indrawing</td><td>80</td><td>72</td><td>81</td><td>71</td><td>2.79</td></tr><tr><td>Crepitation</td><td>63</td><td>82</td><td>84</td><td>60</td><td>2.1</td></tr><tr><td>Chest auscultation</td><td>66</td><td>73</td><td>79</td><td>59</td><td>1.85</td></tr></table></td></tr>
<tr><td>Stoll[275]

<u>Study type:</u> retrospective case series

(chart review)

EL:III</td><td><u>Country:</u>

US

<u>Aim:</u>

To evaluate the incidence of occult bacteraemia (OB) in the era of routine use of heptavalent pneumococcal conjugate vaccine (PCV7).

Setting, inclusion/ exclusion:

They surveyed the medical</td><td>A blood culture was obtained from 631 children 2 to 36 months of age who were not admitted to the hospital at the time of their initial visit. Three hundred two children (48%) were excluded for the following reasons: antibiotic use within 4 days prior to the visit (n = 105), maximum temperature less than 39 °C (n = 133), known or suspected bacterial source other than AOM (n = 44), and increased risk of bacteraemia due to an underlying condition (n = 20). Of the remaining 329 children, results of a complete blood cell count were available for 324 (98%); and results of a manual differential cell count, for 277 (84%).Three blood cultures (0.91%; 95% confidence interval [CI], 0%-1.9%) obtained at the time of evaluation of the 329 episodes yielded a pathogen, all S pneumoniae. The clinical diagnosis in all 3 episodes with bacteraemia was fever without a source. Blood cultures from 4 children (1.2%; 95% CI, 0%-2.4%) yielded contaminants: Streptococcus intermedius, Staphylococcus haemolyticus and Bacillus species, Staphylococcus epidermidis, and *Enterococcus faecalis*. Of the 326 children with negative cultures or contaminants, the clinical diagnoses were fever with no source or a mild upper respiratory tract infection (n = 259); acute gastroenteritis (n = 32); AOM (n = 30); and a recognizable viral syndrome (croup, bronchiolitis, or respiratory symptoms with a positive rapid test for RSV or influenza antigen) (n = 5).</td></tr>
</table>

<table>
<tr><th>Citation/ EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>records of all children 2 to 36 months of age who had a blood culture performed during a visit to the emergency department or urgent care centre of Schneider Children's Hospital (New Hyde Park, NY) between December 11, 2001, and March 5, 2003, a period beginning 16 months after PCV7 was recommended for routine administration to all infants and young children. They analyzed the medical records of the subgroup of children who had a maximum temperature by history or measurement during the visit of at least 39 °C (site of measurement not reported) but were not hospitalized at the time of the visit. We excluded children who had received antibiotics within 4 days prior to the visit because they may have had a falsely negative blood culture. We also excluded children who were diagnosed with a focal bacterial infection other than acute otitis media (AOM) at the initial visit (specifically, urinary tract infection, radiographically confirmed pneumonia, abscess, cellulitis, or lymphadenitis); had blood cultures performed as part of the evaluation for appendicitis, septic arthritis, or intussusception; or had an underlying condition that put them at increased risk for bacteraemia: an immunologic abnormality (sickle cell disease,</td><td>Table : sensitivity, specificity, and predictive values of Lab tests for diagnosis of OB in highly febrile children.
<table><tr><td></td><td>Sensitivity%</td><td>Specificity %</td><td>PPV %</td><td>NPV %</td><td>RR</td></tr><tr><td>WBC>= 15000/µl*</td><td>100</td><td>71</td><td>3.2</td><td>100</td><td>--</td></tr><tr><td>WBC>= 20000/µl*</td><td>100</td><td>88</td><td>7.1</td><td>100</td><td>--</td></tr><tr><td>Bands >=5%**</td><td>33</td><td>56</td><td>0.83</td><td>99</td><td>0.83</td></tr><tr><td>Bands >=10%**</td><td>33</td><td>84</td><td>2.2</td><td>99</td><td>2.2</td></tr><tr><td>ANC>=10000/µl*</td><td>100</td><td>77</td><td>3.8</td><td>100</td><td>--</td></tr><tr><td>ANC>=15000/µl*</td><td>100</td><td>92</td><td>10.7</td><td>100</td><td>--</td></tr><tr><td colspan="6">*: results based on 324 cases; ** : results based on 277 cases.</td></tr></table>
The 3 cases of OB occurred in 2 children. Patient 1 (aged 9 months) was infected with serotype 22F (not included in PCV7). He was treated empirically with an intramuscular dose of ceftriaxone and seen the following day to receive a second dose, at which time he was clinically improved. Patient 2 had 2 episodes of pneumococcal OB 1 month apart, occurring at ages 20 months and 21 months. He had not received PCV7. His first episode was caused by a penicillin-susceptible serotype 4 strain, a serotype included in PCV7. He received intravenous ceftriaxone at the time of the initial visit and an intramuscular dose the following day. When the positive blood culture was reported, he was recalled, another blood culture was obtained, and he was prescribed orally administered cefuroxime. Two days later, the blood culture results remained negative and cefuroxime treatment was discontinued. Twenty-three days after cefuroxime therapy was discontinued, he had a fever without a focus and was treated with intramuscular ceftriaxone. Blood culture yielded S pneumoniae; the isolate was not available for serotyping. The patient was never admitted to Schneider Children's Hospital, however, and further details of his subsequent course are not available.

They found that the 3.2% PPV of a WBC count greater than or equal to 15 000/µL was lower than that observed in each of the 4 pre–Hib conjugate vaccine studies in which this was evaluated (8.7%, 24%, 11%, and 15%) and significantly lower than in 3 of the 4 (P<0.05, chi 2 test).

Table: Comparisons with other studies in the post-Hib Conjugate vaccine, pre-PCV7 Era*.
<table><tr><td></td><td>Lee and Harper[175] (n=9465)</td><td>Alpern[276] (n=5091)</td><td>Badyopadhyay[277] (n=1202)</td><td>Current study (n=329)</td></tr><tr><td>Incidence of OB %</td><td>1.6 (1.3-1.8)</td><td>1.9 (1.5-2.3)</td><td>3.1 (2.2-4.2)</td><td>0.91 (0-1.9)</td></tr></table></td></tr>
</table>

<table>
<tr><th>Citation/ EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>congenital or acquired immunodeficiency), complex congenital heart disease, or the presence of a long-term vascular catheter or a ventriculoperitoneal shunt. We recorded the age, the clinical diagnosis at the time of the visit, and the results of laboratory testing including complete blood cell count and differential cell count, urinalysis, urine culture, blood culture, and antigen testing of nasal washes for respiratory syncytial virus (RSV) and influenza, as well as the results of cultures performed at subsequent emergency department or urgent care visits or hospitalizations within 7 days following the initial visit.</td><td>
<table>
<tr><td>(95%CI)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>PPV for WBC>= 15000/µl, % (95%CI)</td><td>5.1 (4.2-6.1)</td><td>NA</td><td>NA</td><td>3.2 (0-6.7)</td></tr>
<tr><td>PPV for WBC>= 20000/µl, % (95%CI)</td><td>8.1 (6.3-10.4)</td><td>NA</td><td>NA</td><td>7.1 (0-14.9)</td></tr>
<tr><td>Age range, mo</td><td>3-36</td><td>2-24</td><td>2-36</td><td>2-36</td></tr>
<tr><td>Definition of fever (OC)</td><td>39</td><td>39</td><td>39</td><td>39</td></tr>
<tr><td colspan="5">*: case number indicates the number of episodes of high fever.</td></tr>
</table>

They did not determine the number of highly febrile young children who did not have blood obtained for culture; although it was the routine practice of emergency department physicians to obtain blood for culture from such children, the decision to culture was at the discretion of the paediatric emergency department fellow or attending physician.</td></tr>
<tr><td>Mazur[278]

<u>Study type:</u>
Chart review.
EL:III</td><td><u>Country</u>:
USA
<u>Aim:</u>
To determine the frequency and clinical significance of markedly increased WBC counts in children presenting to an ED and, based on those data, to define the degree of leukocytosis which might be considered extreme.
<u>Setting, inclusion/ exclusion:</u>
Texas Children’s Hospital in an urban paediatric hospital which</td><td>There were 29374 visits to the ED during the 6 months period. WBC counts were obtained in 7699 patients (26.2%), and 466 of them had WBC>=25000/µl, for an observed frequency of 5.8%. Charts that could not be located and patients older than 19 yr were excluded.
Records from June to December 1985 had been discarded by the pathology department was not included.
All patients with WBC >=25000/µl (group2, n=424) were identified and paired with the chronologically nearest patient with a WBC between 15000 and 25000µl (group1, n=440).
Age ranged from 1 day to 19 yr (mean:43 months for group1 and 445months for group2).
For further analyses, patients with WBC>=35000/µl, were labelled as group 3 (sub group of group 2).

Table : Ten most common final diagnoses in patients with counts >=25000/µl
<table>
<tr><td>Diagnosis</td><td>Gp2 >=25000/µl, n=44 (%)</td><td>Diagnosis</td><td>Gp3 >=35000/µl, n=44 (%)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Citation/ EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>servers as both primary and tertiary referral centre. All WBC obtained in the ED between February and Many 1985, were reviewed retrospectively.</td><td>
<table>
<tr><td>Pneumonia</td><td>15.2</td><td>Pneumonia</td><td>19.2</td></tr>
<tr><td>Viral syndrome, URI</td><td>11.9</td><td>Viral syndrome, URI</td><td>11.5</td></tr>
<tr><td>Otitis media</td><td>8.9</td><td>Bacteraemia</td><td>10.3</td></tr>
<tr><td>Bacteraemia</td><td>6.1</td><td>Gastroenteritis</td><td>6.4</td></tr>
<tr><td>Reactive airway disease</td><td>5.5</td><td>Sickle cell disease</td><td>6.4</td></tr>
<tr><td>Gastroenteritis</td><td>5.2</td><td>Leukaemia</td><td>6.4</td></tr>
<tr><td>Sickle cell disease</td><td>4.5</td><td>Otitis media</td><td>5.1</td></tr>
<tr><td>Abscess, cellulites</td><td>4.5</td><td>UTI</td><td>5.1</td></tr>
<tr><td>UTI</td><td>3.4</td><td>Diabetic ketoacidosis</td><td>2.6</td></tr>
<tr><td>Trauma</td><td>3.4</td><td>Abscess, cellulites</td><td>2.6</td></tr>
<tr><td>Total</td><td>68.6</td><td>Total</td><td>75.6</td></tr>
</table>

There were 227 children whose initial diagnosis was fever alone with trivial infections, among them, there was a significantly increased risk of bacteraemia with increased WBC count; p=0.04 and p=0.0.2 for group 2&3 when compared with group1. There were 26 (8.7%) patients with WBC>=35000/µl and 6 had serious outcomes: 5 bacteraemia and 1 UTI. Of those 103 patients with WBC>=25000/µl and <35000/µl, 10 (9.7%) were bacteraemic.

Table : clinical outcomes with calculated risk estimates and 90%CI
<table>
<tr><td rowspan="2">Clinical outcome</td><td rowspan="2">Gp1 >=15000/µl & <25000/µl (%)</td><td colspan="3">Gp2 >=25000/µl</td><td colspan="3">Gp3 >=35000/µl,</td></tr>
<tr><td>%</td><td>Risk estimate</td><td>95%</td><td>%</td><td>Risk estimate</td><td>95%</td></tr>
<tr><td>Admitted to hospital</td><td>61</td><td>72</td><td>1.66</td><td>1.24-2.22</td><td>77</td><td>2.14</td><td>1.20-3.81</td></tr>
<tr><td>Proven bacterial infection</td><td>11</td><td>17</td><td>1.58</td><td>1.06-2.36</td><td>26</td><td>2.70</td><td>1.47-4.94</td></tr>
<tr><td>Bacteraemia</td><td>3</td><td>6</td><td>2.24</td><td>1.08-4.63</td><td>10</td><td>3.92</td><td>1.49-10.3</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/ EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Serious disease</td><td>12</td><td>18</td><td>1.55</td><td>1.04-2.30</td><td>26</td><td>2.52</td><td>1.38-4.61</td></tr>
</table>
</td></tr>
<tr><td>Hatherill[279]

<u>study type:</u>
prospective cohort study (PICU population)
EL: III</td><td><u>Country:</u>
UK
<u>Aim:</u>
To evaluate diagnostic markers of infection in critically ill children, comparing procalcitonin with C reactive protein and leukocyte count in a paediatric intensive care unit (PICU).
<u>Setting, inclusion/ exclusion:</u>
Over an 18 month period, 175 children, median age 16 months (range, 0.03-193), were enrolled in the study on admission to the paediatric intensive care unit (PICU). Forty six patients (26%) were aged less than 3 months, and 64 (37%) between 3 and 36 months. Most children (n = 156; 89%) were admitted by a PICU retrieval team, within 24 hours of hospital presentation. Patients were excluded if they had received parenteral antibiotics in the past seven days (except within the preceding 24 hours) or if they had undergone surgery.</td><td>Table : The aetiology in 77 patients with septic shock
<table>
<tr><th>Aetiology</th><th>Prevalence</th></tr>
<tr><td>Gram negative</td><td></td></tr>
<tr><td>Neisseria meningitidis</td><td>37</td></tr>
<tr><td>Haemophilus influenzae</td><td>1</td></tr>
<tr><td>Escherichia coli</td><td>5</td></tr>
<tr><td>Enterobacter spp</td><td>1</td></tr>
<tr><td>Klebsiella spp</td><td>1</td></tr>
<tr><td>Pseudomonas spp</td><td>2</td></tr>
<tr><td>Pasteurella spp</td><td>1</td></tr>
<tr><td>Gram positive</td><td></td></tr>
<tr><td>Group B streptococcus</td><td>6</td></tr>
<tr><td>Pneumococcus</td><td>1</td></tr>
<tr><td>α-Haemolytic streptococcus</td><td>1</td></tr>
<tr><td>Streptococcus viridans</td><td>1</td></tr>
<tr><td>Streptococcus pyogenes</td><td>1</td></tr>
<tr><td>Enterococcus</td><td>2</td></tr>
<tr><td>Coagulase negative staphylococcus</td><td>5</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/ EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>Children were classified according to their clinical and laboratory data into one of five categories: non-infected controls -- for example, toxin ingestion, trauma, or seizures (n = 43; 25%); viral infection (n = 14; 8%); localised bacterial infection without shock -- for example, pneumonia, tracheitis, or urinary tract infection (n = 25; 14%); bacterial meningitis/encephalitis (two patients with mycoplasma encephalitis were included in this group) (n = 10; 6%); and septic shock (n = 77; 44%).

Septic shock was defined as hypotension or poor capillary refill responding to fluid or pharmacological intervention, in the presence of hyperthermia or hypothermia, tachycardia, and tachypnoea, in addition to at least one of the following: acute mental changes, hypoxaemia, hyperlactataemia, or oliguria. In addition to these features, evidence of infection was required for final inclusion in the category of septic shock – for example, bacteriological isolate (not necessarily positive blood culture); characteristic meningococcal or staphylococcal rash; or cerebrospinal, bronchoalveolar, or peritoneal fluid profile consistent with bacterial infection. Six children (3%) who were enrolled</td><td>
<table>
<tr><td>Staphylococcus aureus</td><td>2</td></tr>
<tr><td>Fungal</td><td></td></tr>
<tr><td>Candida albicans</td><td>3</td></tr>
<tr><td>Other</td><td></td></tr>
<tr><td>Peritonitis</td><td>2</td></tr>
<tr><td>Pancreatic abscess</td><td>1</td></tr>
<tr><td>Toxic shock syndrome</td><td>3</td></tr>
<tr><td>Osteomyelitis</td><td>1</td></tr>
</table>
Procalcitonin differed significantly across the five categories of infection (p < 0.0001; Kruskal-Wallis). Procalcitonin was higher in children with septic shock compared with all other groups (p < 0.001; Dunn's) except bacterial meningitis. Procalcitonin was significantly higher in bacterial meningitis compared with viral infection and controls (p < 0.05 and 0.001, respectively). In the subgroup of children with meningococcal disease (n = 37; 21%) admission procalcitonin was no higher (median, 104 ng/ml; range, 7.7-760) than in non-meningococcal septic shock (median, 92 ng/ml; range, 3.3-736; p = 0.32). Separate post hoc analysis of the six patients with presumed septic shock excluded from further comparison showed a median procalcitonin of 182.5 ng/ml (range, 5.1-500), comparable to that of the septic shock group.

Table Admission procalcitonin (PCT), C reactive protein (CRP), and leukocyte count (WCC) values for all children
<table>
<tr><th></th><th>Septic shock (n = 77)</th><th>Bacterial meningitis (n = 10)</th><th>Localised bacterial infection (n = 25)</th><th>Viral infection (n = 14)</th><th>Non-infected controls (n = 43)</th></tr>
<tr><td>PCT (ng/ml)</td><td>94.6 (3.3-759.8)</td><td>25.5 (7.2-118.4)</td><td>2.9 (0-24.3)</td><td>0.8 (0-4.4)</td><td>0 (0-4.9)</td></tr>
<tr><td>CRP (mg/l)</td><td>101 (3-335)</td><td>110.5 (32-353)</td><td>20 (7-213)</td><td>12 (7-76)</td><td>8 (2-47)</td></tr>
<tr><td>WCC (× 10^9/l)</td><td>12.1 (0.4-83.8)</td><td>18.2 (2-33.5)</td><td>9.7 (1.4-30.4)</td><td>5.75 (2.5-32)</td><td>13.7 (2.4-25.3)</td></tr>
<tr><td colspan="6">Values are median (range).</td></tr>
</table>
C reactive protein also differed significantly across the five categories of infection (p < 0.0001; Kruskal-Wallis) and was higher in septic shock compared with localised bacterial, viral infection, and controls (p < 0.01, 0.01, and 0.001, respectively), but not bacterial meningitis. However, C reactive protein did distinguish bacterial meningitis from localised bacterial and viral infection (p < 0.05 and 0.01, respectively). The leukocyte count did not differ significantly across the five categories of infection (p = 0.39;</td></tr>
</table>

<table>
<tr><th>Citation/ EL</th><th>Methodology</th><th>Effect size</th></tr>
<tr><td></td><td>with diagnoses of presumed septic shock, but who subsequently had no documented focus of infection, were excluded from the group analysis and evaluated separately</td><td>Kruskal-Wallis).

Table Sensitivity, specificity, positive and negative predictive values (%) of admission PCT and CRP values for septic shock
<table>
<tr><th>Screening value</th><th>Sensitivity</th><th>Specificity</th><th>PPV %</th><th>NPV %</th><th>Relative risk</th></tr>
<tr><td>PCT > 2 ng/ml</td><td>100</td><td>62</td><td>69</td><td>100</td><td>--</td></tr>
<tr><td>PCT > 5 ng/ml</td><td>99</td><td>78</td><td>79</td><td>99</td><td>79.0</td></tr>
<tr><td>PCT > 10 ng/ml</td><td>88</td><td>84</td><td>82</td><td>90</td><td>8.20</td></tr>
<tr><td>PCT >20 ng/ml</td><td>83</td><td>92</td><td>90</td><td>87</td><td>30.0</td></tr>
<tr><td>CRP > 20 mg/l</td><td>91</td><td>62</td><td>66</td><td>89</td><td>6.00</td></tr>
<tr><td>CRP > 30 mg/l</td><td>81</td><td>70</td><td>69</td><td>82</td><td>3.83</td></tr>
<tr><td>CRP > 40 mg/l</td><td>79</td><td>77</td><td>74</td><td>82</td><td>4.11</td></tr>
<tr><td>CRP >50 mg/l</td><td>76</td><td>80</td><td>76</td><td>80</td><td>3.80</td></tr>
<tr><td>PCT > 2 ng/ml
and
CRP > 20 mg/l</td><td>91</td><td>78</td><td>78</td><td>91</td><td>8.67</td></tr>
<tr><td>PCT > 20 ng/ml
and
CRP > 50 mg/l</td><td>69</td><td>92</td><td>88</td><td>78</td><td>4.00</td></tr>
<tr><td colspan="6">Optimum diagnostic cut off values derived from the ROC curve are shown in bold.

CRP, C reactive protein; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value; ROC, receiver operating characteristic.</td></tr>
</table>
The range of procalcitonin concentrations in children with bacterial meningitis (range, 7.2-118.4 ng/ml) overlapped that of septic shock (range, 3.3-759.8 ng/ml). Because it is clinically important to differentiate these patients from those with less serious bacterial disease, we then combined both bacterial meningitis and septic shock to form an additional category termed "severe bacterial infection". Further analysis was performed for sensitivity and specificity in identifying children with severe bacterial infection, yielding an area under the ROC curve of 0.98 (95% CI, 0.96 to 1.0) for procalcitonin. Note that procalcitonin > 2 ng/ml also had 100% sensitivity and a negative predictive value for severe bacterial infection, but with a specificity and positive predictive value of 70% and 78%, respectively.</td></tr>
</table>

Chest radiography

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr>
<td>Swingler[179]

Study type:
(Systematic review)
EL 1b</td>
<td>Aim:
A systematic review to quantify the accuracy of chest radiography in differentiating bacterial from viral lower respiratory infection in Children.
Methodology
Relevant studies were identified according to the following criteria:
1.Assessment of the Radiographic differentiation of bacterial from viral pneumonia.
2.Studies of children under 18yrs, or studies from which data on children less than 18yrs could be extracted.
3. Use of credible reference standards for bacterial and viral infection.
4. Independent and blind assessment of radiographic and reference standards
5. Studies of a clinical population who would normally be tested for the disorder(as opposed to patients already known to have bacterial pneumonia being compared with controls from other population).
Exclusions:
1.Infections by Chlamydia and Mycoplasma, which are neither bacteria nor viruses</td>
<td>13 relevant studies were identified, of which 5 met the inclusion criteria. Characteristics of study design and methods of data collection and reporting are shown in the table below.

Table : characteristics of study and methods of data collection and reporting

<table>
<tr><th></th><th>Present(%)</th><th>Absent</th><th>Unclear</th></tr>
<tr><td>Eligibility criteria</td><td></td><td></td><td></td></tr>
<tr><td>Credible reference standard</td><td>7(54)</td><td>6</td><td></td></tr>
<tr><td>Same reference Standard applied positive and negative test results</td><td>13(100)</td><td>0</td><td></td></tr>
<tr><td>Independent blind comparison of Test result with reference standard</td><td>7(54)</td><td>0</td><td>6*</td></tr>
<tr><td>Clinical study population(not case Control design)</td><td>13(100)</td><td>0</td><td></td></tr>
<tr><td>Other quality criteria</td><td></td><td></td><td></td></tr>
<tr><td>All tests verified by reference standard</td><td>2(15)</td><td>7</td><td>4</td></tr>
<tr><td>Prospective data collection</td><td>2(15)</td><td>7</td><td>4</td></tr>
<tr><td>Consecutive patients</td><td>4(31)</td><td>1</td><td>8</td></tr>
<tr><td>Description of study population (2 Of age M:F ratio and clinical features)</td><td>4(31)</td><td>9</td><td></td></tr>
<tr><td>Description of reference standards (definition of positive and negative results)</td><td>11(85)</td><td>2</td><td></td></tr>
<tr><td>Description of Test (definition of positive And negative results)</td><td>10(77)</td><td>3</td><td></td></tr>
<tr><td>Test interpreted without clinical information</td><td>7(54)</td><td>4</td><td>2</td></tr>
<tr><td>Clinically meaningful measures of test Accuracy (sensitivity or specificity or Predictive values or likelihood ratios)</td><td>4(31)</td><td>9</td><td></td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>2. Cases with no demonstrated aetiology.</td><td>
<table>
<tr><td>Confidence intervals for measures of Test accuracy</td><td>0(0)</td><td>13</td><td></td></tr>
<tr><td>Assessment of observer variability</td><td>4(31)</td><td>9</td><td></td></tr>
</table>

Table :Characteristics of the 5 included studies are shown in the table below
<table>
<tr><td colspan="6">Characteristics of included studies</td></tr>
<tr><td></td><td>Subjects</td><td>Observers</td><td>Etiological Profile</td><td>Bacterial reference standard</td><td>Viral reference standard</td></tr>
<tr><td>McCarthy 1981</td><td>128 consecutive children seen in an emergency room with infiltrates on chest radiography</td><td>1 general paediatrician
1 paediatric radiologists
1 general radiologists</td><td>Viral(16)
Bacterial(5)
Mycoplasma(9)
Unknown(98)</td><td>Blood or pleural fluid culture</td><td>Rising antibody titre</td></tr>
<tr><td>Khamapirad, 1987</td><td>62 children hospitalized with LRTI</td><td>Radiologist and clinician-epidemiologist viewing films together</td><td>Viral(44)
Bacterial(18)</td><td>Blood or pleural fluid culture</td><td>Rising antibody titre or nasopharyngeal culture</td></tr>
<tr><td>Bettenay
1988</td><td>107 children aged>100days with strong clinical evidence of pneumonia. In patients and out patients</td><td>2 radiologists viewing films together</td><td>Bacterial(11)
Viral(47)
Unknown or
Data incomplete(49)</td><td>Culture(blood or pleural fluid) or antigen in urine</td><td>Nasopharyngeal antigen or culture</td></tr>
<tr><td>Courtoy
1989</td><td>36 children with chest radiograph and etiologic diagnosis of pneumonia of 98</td><td>2 paediatricians
2 paediatric radiologists
1 paediatric</td><td>Viral(24)
Bacterial(120
Unknown or data</td><td>Blood culture or urine antigen</td><td>Rising antibody titre or nasopharyngeal antigen or culture</td></tr>
</table>
</td></tr>
</table>

Citation/EL	Methodology	Results

	paediatric outpatients	immunologists	incomplete(62)		
Korppi 1993	127 children hospitalized with definite alveolar or interstitial pneumonia	2 radiologists (viewing films together?)	Bacterial(20) Viral(20) Mixed(21) Unknown or data incomplete(66)	Rising antibody titre or antigen in serum or urine	Rising antibody titre or nasopharyngeal antigen

The following bacterial and viral reference standards were included, alone or in combination:

-Culture of bacteria form bronchoalveolar lavage, lung aspirate, or lung biopsy

-Culture of bacteria from blood or pleural fluid

-detection of bacterial antigen or DNA in blood or urine

-Rising antibody titre to a specific bacterium.

-Nasopharyngeal viral culture

-Viral antigen detected in nasopharyngeal secretions,

-Rising antibody titre to a specific virus.

Measures of Test accuracy in the detection of bacterial infection are shown in the table below, with best results occurring in Khamapirad 1987 study which adapted a scoring system that included both clinical and laboratory data. Likelihood ratios ranged form1.1 to5.6 for a positive test and from 0.13 to 0.90 for a negative test. Sensitivity and specificity not calculated due to indeterminate readings in Bettenay 1988, which were excluded or not reported therefore test accuracy was reported as over estimated.

Clinical information was not reported in 3 of the studies(Bettenay 1981,Korppi 1993, and McCarthy 1981). Amongst these 3 studies, the highest likelihood ratios for a positive test was 2.0 and 0.40 for a negative test.

Table ：Test accuracy of included studies.

				Likelihood ratio(95%CI)		
	n	Sensitivity (95% CI)	Specificity (95%CI)	Positive test	Indeterminate	Negative test
McCarthy	21	60-80%	No data			

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>1981</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Khamapirad 1987</td><td>62</td><td>89%(65-99%)</td><td>84%(70-93%)</td><td>5.6(2.8-11.2)</td><td></td><td>0.13(0.05-0.32)</td></tr>
<tr><td>Bettenay 1988</td><td>58</td><td></td><td></td><td>2.0(1.1-3.6)</td><td>1.4(0.46-4.41)</td><td>0.40(0.12-1.3)</td></tr>
<tr><td>Courtoy 1989</td><td>36</td><td>42-58%</td><td>54-83%</td><td>1.1-3.4</td><td></td><td>0.5-0.9</td></tr>
<tr><td>Korppi 1993</td><td>61</td><td>49%(33-65%)</td><td>65%(41-85%)</td><td>1.4(0.71-2.7)</td><td></td><td>0.78(0.52-1.2)</td></tr>
</table>
</td></tr>
<tr><td>Virkki[180]

<u>Study type:</u>
Prospective Cohort.

EL: II</td><td><u>Country:</u>

Finland

<u>Aim:</u>

To investigate the differential diagnostic role of chest radiographic findings, total WBC, ESR, and serum C reactive protein in children with community acquired pneumonia of varying aetiology.

<u>Settings, Inclusion/exclusions</u>

296 consecutive children admitted into the hospital with community acquired pneumonia, were enrolled between 1Jan 1993 and Dec 1995. Based on a radiological diagnosis of an infiltrate on the chest radiograph, and fever of >37.5º and respiratory symptoms. PA and lateral chest radiographs obtained and viewed by</td><td>Viral infection alone was seen in 32% of patients,22% in bacterial infections alone and 30% mixed.

Comparisons between bacterial infections(n=134), sole bacterial infections +mixed bacterial/viral infections) and sole viral infections(n=81) are shown below. No significant result between bacterial and mixed bacterial/viral infections(Results not reported).

The 215 patients were divided into 2 groups of <2 yrs and >=2yrs. Radiological findings revealed for those greater than 2 yrs,78%(n=65) of those with bacterial infection had alveolar infiltrates compared with 56%(n=18) of those with viral infections (p=0.02). Alveolar infiltrate was lobar in 36% of cases with bacterial pneumonia and in 15% of those with viral pneumonia.(p=0.001). In children with solely viral pneumonia,49% had alveolar changes, compared with bacterial pneumonias(p=0.001).

Table : Chest radiographic findings in 215 children with community acquired pneumonia
<table>
<tr><th></th><th>Total n(%)</th><th>Total bacterial n(%)</th><th>Exclusive Viral n(%)</th><th>P value</th><th>Sensitivity (Bacterial)</th><th>Specificity (bacterial)</th></tr>
<tr><td></td><td>215(100)</td><td>134(100)</td><td>81(100)</td><td></td><td></td><td></td></tr>
<tr><td><2yrs of age</td><td>100(47)</td><td>51(38)</td><td>49(60)</td><td>NS</td><td>0.38</td><td>0.40</td></tr>
<tr><td>>=2yrs of age</td><td>115(53)</td><td>83(62)</td><td>32(40)</td><td>0.001</td><td>0.62</td><td>0.60</td></tr>
</table>
</td></tr>
</table>

Citation/EL	Methodology	Results
	3 radiologists (Independently but no report of blinding) were classified as; 1.alveolar and/or interstitial pneumonic changes, hyperaeration, hilar enlargement, atelectatsis, pleural fluid, location in the lung or both lungs. Patients were accepted if at least 2 radiologist agreed, with X rays which was re-reviewed by 1 radiologist to determine if infiltrate was lobar or multilobar. Viral tests were performed using nasopharyngeal aspirates to detect viral antigens (Influenza A and B, RSV, parainfluenza types 1,2 and 3 and adenovirus) using time resolved fluoroimmunoassay using monoclonal antibodies. Enzyme immunoassay(EIA) was used to determine virus specific serum antibodies. For bacteria, EIA were used to measure IgG antibodies to pneumococcal pneumolysin and C-polysaccharide. Antibody assays were performed on acute and convalescent samples. For Non typeable *Haemophilus influenzae and Moraxella catarrhalis* EIA using whole bacterial antigen. IgM and G for Chlamydia infections were studies by a microimmunofluorescence method using elementary antibodies of *Chlamydia pneumoniae* Kajaani7 and *C. trachomatis* 1.2 as antigens.	<table><tr><td>Alveolar infiltrates <2yrs of age >=2yrs of age</td><td>137(64) 54(25) 83(39)</td><td>97(72) 32(24) 65(49)</td><td>40(49) 22(27) 18(22)</td><td>0.001 NS 0.02</td><td>0.72 0.63 0.78</td><td>0.51 0.55 0.44</td></tr><tr><td>Lobar alveolar infiltrates <2yrs of age >=2yrs of age</td><td>60(28) 15(7) 45(21)</td><td>48(36) 13(10) 35(26)</td><td>12(15) 2(2) 10(12)</td><td>0.001 0.003 NS</td><td>0.37 0.25 0.44</td><td>0.85 0.96 0.68</td></tr><tr><td>Exclusively interstitial infiltrates <2yrs of age >=2yrs of age</td><td>77(36) 45(21) 32(15)</td><td>37(28) 19(14) 18(13)</td><td>40(49) 26(32) 14(17)</td><td>0.001 NS NS</td><td>0.49 0.53 0.44</td><td>0.72 0.63 0.78</td></tr><tr><td>Hyperaeration Atelectatsis Enlarged Lymph nodes Pleural fluid</td><td>83(39) 19(9) 24(11) 12(6)</td><td>47(35) 10(7) 13(10) 8(6)</td><td>36(44) 9(11) 11(14) 4(5)</td><td>NS NS NS NS</td><td>0.44 0.07 0.10 0.06</td><td>0.65 0.89 0.86 0.95</td></tr></table> Lab findings showed increased WBC(>15.0x10*9/L) or increased ESR(>30mm/h) was similar in bacterial and viral pneumonia (48% v47% and 66% v 60%),respectively). There was also Significant differences in the CRP levels between the two groups at selected levels of >40mg/l (p=0.004), >80mg/l (p=0.001),>120mg/l (p=0.001), and 160mg/l(p=0.01). A screening limit of >80mg/l was chosen for CRP concentration for bacterial pneumonia (sensitivity 0.52,specificity 0.72) as a result of too many false positives at the level of >40mg/l(specificity 0.53) and too many false negatives at the level of >120mg/l (sensitivity 0.36). A CRP concentration of>80mg/l significantly predicted bacterial pneumonia in the younger age group(<2yrs) compared to the

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr><td></td><td>IgM antibodies to mycoplasma pneumoniae were measures using a commercial kit EIA with minor modifications(Platelia; sanofidiagnostics PasteurSA, Marnes la Coquette, France)

42 children were excluded due to chest radiographs not available for review or no infiltrate found(n=9),convalescent serum not obtained (n=33).</td><td>older one(P=0.003)

In combined radiographic and laboratory findings, significant differences between bacterial and viral pneumonia included a CRP concentration of >80mg/l.(P values not given)

Table : Laboratory findings and combinations of chest radiographic and laboratory findings in 215 children with community acquired pneumonia.

<table>
<tr><th></th><th>Total n(%)</th><th>Total bacterial n(%)</th><th>Exclusively viral n(%)</th><th>P value</th><th>Sensitivity (bacterial)</th><th>Specificity (bacterial)</th></tr>
<tr><td></td><td>215(100)</td><td>134(100)</td><td>81(100)</td><td></td><td></td><td></td></tr>
<tr><td>WBC.15.0x10^9 /l</td><td>102(47)</td><td>64(48)</td><td>38(47)</td><td>NS</td><td>0.48</td><td>0.53</td></tr>
<tr><td>ESR>30mm/h</td><td>137(64)</td><td>88(66)</td><td>49(60)</td><td>NS</td><td>0.66</td><td>0.40</td></tr>
<tr><td>CRP<20mg/l</td><td>57(27)</td><td>30(22)</td><td>27(33)</td><td>NS</td><td>0.33**</td><td>0.78**</td></tr>
<tr><td>CRP>40mg/l</td><td>127(59)</td><td>89(66)</td><td>38(47)</td><td>0.004</td><td>0.66</td><td>0.53</td></tr>
<tr><td>CRP>80mg/l</td><td>93(43)</td><td>70(52)</td><td>23(28)</td><td>0.001</td><td>0.52</td><td>0.72</td></tr>
<tr><td><2yrs of age</td><td>23(11)</td><td>18(13)</td><td>5(6)</td><td>0.003</td><td>0.35</td><td>0.90</td></tr>
<tr><td>>=2yrs of age</td><td>70(33)</td><td>52(39)</td><td>18(22)</td><td>NS</td><td>0.63</td><td>0.44</td></tr>
<tr><td>CRP>120mg/l</td><td>60(28)</td><td>48(36)</td><td>12(15)</td><td>0.001</td><td>0.36</td><td>0.85</td></tr>
<tr><td>Alveolar infiltrates* & CRP>80mg/l</td><td>80(37)</td><td>62(46)</td><td>18(22)</td><td>0.001</td><td>0.46</td><td>0.78</td></tr>
<tr><td colspan="7">* Includes mixed interstitial and alveolar infiltrates. ** sensitivity and specificity for viral pneumonia</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/EL</th><th>Methodology</th><th>Results</th></tr>
<tr>
<td>Heulitt[280]

Study type:

Retrospective Cohort

EL III</td>
<td>Country:

USA

Aim:

To evaluate the necessity of obtaining chest radiographs in febrile infants less than 3 months old.

Settings, Inclusion/exclusion criteria:

Between July 1981 and December 1985, the records of 192 infants, less than 3 months old, with a rectal temp greater than 100.5 °F were retrospectively reviewed. All infants were admitted to the hospital, treated with parenteral antibiotics for a minimum of 48hrs and underwent the following work up: Complete blood count(WBC+ differential), urinalysis, CSF evaluation including cell count, glucose and protein levels, blood and urine cultures, CSF specimen and AP and lateral chest radiography.

Inclusion: chest radio graphs included were reviewed by 2 paediatric radiologists who were blinded to the patient’s clinical history. Hospital records were reviewed and the following information were abstracted: age, sex, presenting signs and symptoms, RR, positive finding on physical examination, temperature and hospital course.</td>
<td>Final diagnoses for all 192 infants included Fever without source (n=38), Upper respiratory tract Infection (n=24), viral syndrome (n=24), otitis media(n=21), gastroenteritis (n=16), UTI (n=13), Pneumonia (n=12), aseptic meningitis with white blood count in CSF greater than 10cells/mm^3, conjunctivitis (n=5), bacteraemia (n=5) and salmonella enteritis (n=3) bacterial meningitis (n=2), hepatitis (n=2), osteomyelitis (n=2) and viremia (n=1).

Patients were categorized according to whether or not signs of Respiratory distress (RD) were present. RD was found in 19 patients, of which 7 had positive findings on radiograph (Slight-1,moderate-4, and severe-2). Findings on the chest radiograph were considered gold standard, the sensitivity of signs of respiratory distress in detecting presence of a parenchymal density(patients with respiratory distress and positive findings on radio graph) was 58%. The positive predictive value was 37% and negative predictive value was 97%. Prevalence of positive findings on chest radiograph in febrile infants less than 3 months was 6%, therefore only a small proportion (3%) of the infants without respiratory distress had positive findings on the radiograph.

Table : Classification of radiographic findings
<table>
<tr><th>Class</th><th>Findings</th></tr>
<tr><td>I</td><td>Negative</td></tr>
<tr><td>A</td><td>No pathologic findings.</td></tr>
<tr><td>B</td><td>Questionable parenchymal density</td></tr>
<tr><td>II</td><td>Slight</td></tr>
<tr><td>A</td><td>One small subsegmental parenchymal density</td></tr>
<tr><td>B</td><td>Minimal peribronchial thickening</td></tr>
<tr><td>III</td><td>Moderate</td></tr>
<tr><td>A</td><td>2 or more subsegmental parenchymal densities</td></tr>
<tr><td>B</td><td>1 or more segmental parenchymal densities</td></tr>
<tr><td>C</td><td>I small parenchymal density with severe hyperinflation or localised air trapping</td></tr>
<tr><td>D</td><td>Central interstitial changes with moderate or severe hyperinflation</td></tr>
<tr><td>E</td><td>Diffuse mild interstitial changes and peribronchial thickening.</td></tr>
</table>
</td>
</tr>
</table>

Citation/EL	Methodology	Results

IV	Severe
A	Lobar opacification
B	Diffuse interstitial changes with at least 1 subsegmental parenchymal density
C	Diffuse parenchymal densities(every lobe) with or without interstitial changes.
D	Severe lobar atelectatsis with parenchymal density else where
	Severe diffuse interstitial changes
E	Parenchymal densities and pleural fluids

Table : Sensitivity, specificity and predictive values. For correlations of respiratory signs (Respiratory distress) and radiographic findings(reference standard)

sensitivity	Specificity	PPV %	NPV %	Relative risk	Prevalence(%)
58	93	37	97	12.3	6

Table : Correlation of respiratory signs and radiographic findings.

Respiratory Signs	Radiographic findings	
	Positive	Negative
Positive	7	12
Negative	5	168

Patients in groups with and without respiratory signs were analyzed with regard to age, temperature, WBC count, and progress

Citation/EL	Methodology	Results
		while in the hospital. Positive findings on chest radiographs were more frequent in patients more than 60 days old (p=0.02). There were no association between positive findings on radiographs and a WBC count greater than 12,000/mm^3(12.0x10^9/L)(p=0.06) or a temperature greater than 102ºF(rectal)(p=0.79). Although a measurement of the severity of illness is limited in a retrospective study, length of hospital stay was measured as a proxy (suspected to be a post hoc calculation) The mean hospital stay was longer for the patients with positive findings on radiographs and signs of respiratory distress than for patients with negative findings on radiographs and no signs of respiratory distress(p=0.0001). There was also no difference in the mean hospital stay of patients with positive findings on radiographs and no signs of respiratory distress and patients with negative findings on radiograph and no signs of respiratory distress.

Response to Antipyretics

Citation/ EL	Method	Results
Weisse[184] Study type: Prospective cohort study EL: 2+	Country: USA Aim: To test the hypothesis that there would be no difference in antipyretic response between viral and bacterial infections. Method, inclusion/ exclusion: This study was conducted from September 1985 to October 1986 in the Pediatric service at Brooke Army Medical Centre. The study population consisted of patients aged 0-18 years who presented with an oral or rectal temperature of 102 ^{O}F (38.9^{O}C) or greater. Patients were excluded if they were already receiving antibiotic therapy or had received an antipyretic within 3 hours of presentation. After having informed consent, the patients were given acetaminophen, 15 mg/ kg to a maximum dose of 650 mg, and their temperature rechecked by the same method after 1 hour.	One hundred patients were enrolled, age ranged from 9 days to 17 years with median of 2 years. Blood specimens were obtained from 81 patients, WBC in 79 and viral studies in 65 patients. 16 patients had viral illness and 17 had bacterial illness. The mean temperature change was -1.16^{o}F for the viral group and -1.48^{o}F for the bacterial group and these two are not significantly different (p=0.37). Of the 100 patients 4 in the bacterial group and 10 in the viral group became afebrile and the difference is not significant (chi^{2}=0.00474, p value not reported).

<table>
<tr>
<td>Torrey[185]

Study type:
Prospective cohort study
EL: 2+</td>
<td>Country:
USA
Aim:
To test the hypothesis that antipyretic therapy is less effective in lowering body temperature in patients with bacteraemia
Method, inclusion/ exclusion:
Patients seen in ED of the Children’s Hospital in Philadelphia from July 1980 to March 1981, who were aged 3-24 months, and had initial temperatures 38.9 °C or higher were included. Children with serious focal infections necessitating admission to the hospital were excluded. Temperature readings were obtained rectally using electronic thermometers with a digital read-out.
All patients received 10 mg/kg of acetaminophen or aspirin at the time of initial recording of temperature (T1). A second reading was obtained after 60-120 min (T2) (time not specified).</td>
<td>They found 516 eligible patients and 255 of them completed the study. None of them had serious underlying disease. 16/255 (6.7%) had occult bacteraemia.
Table : comparison of bacteraemic and non-bacteraemic groups
<table>
<tr><th></th><th>Bacteraemia (n=16)</th><th>Non-bacteraemia (n=239)</th><th>P value</th></tr>
<tr><td>Mean age (mo)</td><td>10.8</td><td>11.5</td><td>0.31</td></tr>
<tr><td>Mean T1</td><td>40.1</td><td>39.9</td><td>0.04</td></tr>
<tr><td>T1>40 °C (%)</td><td>8(50)</td><td>118 (49)</td><td>0.76</td></tr>
<tr><td>Mean T2</td><td>38.8</td><td>38.8</td><td>0.46</td></tr>
<tr><td>Mean change of temperature</td><td>1.32</td><td>1.05</td><td>0.14</td></tr>
</table>
There was no significant difference between bacteraemia and non-bacteraemia children for either T2 (p=0.46) or mean change of temperature (p=0.14).</td>
</tr>
</table>

<table>
<tr>
<td>Baker[162]

Study type:
Prospective cohort study
EL: 2+</td>
<td>Country:
USA
Aim:
To investigate the effects of fever reduction on the clinical appearance of infants at risk for occult bacteraemia
Methods, inclusion/ exclusion:
Patients were enrolled from the ED of the Children’s Hospital from September 1986 to January 1988, on a non-selected, non-consecutive basis (convenience study). Entry criteria were infants of (1) 3-24 months old, (2) temperature > 39.4 °C, (3) no antibiotics use in the previous 48 hours. Infants with overt signs of meningitis (pain with forward flexion of the neck, nuchal rigidity, bulging fontanel, positive Brudzibnski or Kering signs) or septic shock were excluded. Prior use of acetaminophen did not exclude patients from this study.</td>
<td>During the study period, 154 patients were enrolled, the average age was 12 months (ranged from 3-23 months). 13 of them had bacteraemia.
They found no correlation between fever reduction with acetaminophen and underlying serious bacterial illness (p values not reported).

Table : Accuracy of YOS > 10 to predict serious bacterial illness
<table>
<tr><th></th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>PPV (%)</th></tr>
<tr><td>Before fever reduction</td><td>68</td><td>77</td><td>30</td></tr>
<tr><td>After fever reduction</td><td>21</td><td>92</td><td>27</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>Yamamoto[186]

Study type:

Prospective cohort study

EL:2 +</td>
<td>Country

USA

Aim:

To test the hypothesis that children whose fevers fail to respond to antipyretic therapy are more likely to be bacteraemic than children whose fever are lowered by antipyretic measures.

Methods, inclusion/ exclusion:

All children presenting to the ED of two Hospitals aged from three to 24 months of age with rectal temperatures of greater than or equal to 40.0 degrees C (104.0 degrees F) and did not take antibiotics were included.

After temperature was taken, patient was treated according to a pre-defined dose. Children who had not received an antipyretic within 4 hours of presentation were given 10-15 mg/kg of acetaminophen. Children who had received an antipyretic within 2-4 hours of presentation were given a different drug.</td>
<td>There were 332 patients eligible for the study, and 233 were available to analysis. Children from two clinical settings were studied: primarily black lower-class children at an inner-city hospital (n = 188) and primarily white middle-class children at a suburban hospital (n = 45).

They found an overall prevalence of bacteraemia of 7.3%, which was not statistically different between two hospitals. A response to antipyretic therapy, defined as a decrease in temperature of at least 1 degrees C, was seen in 83.7% of children. There was no relationship between results of blood culture and response to antipyretics (see table below).

Table : Temperature response to antipyretics for bacteraemic and non-bacteraemic children
<table>
<tr><th rowspan="2">Time</th><th>No. non-responders</th><th>No. non-responders</th><th rowspan="2">P</th></tr>
<tr><th>No + BC*</th><th>No – BC*</th></tr>
<tr><td>Overall (n=233)</td><td>2/17 (11.8%)</td><td>36/216 (16.7%)</td><td>0.598</td></tr>
<tr><td>60-89 min (n=156)</td><td>2/12 (16.7%)</td><td>48/144 (33.3%)</td><td>0.235</td></tr>
<tr><td>90-119 min (n=158)</td><td>2/12 (16.7%)</td><td>32/146 (21.9%)</td><td>0.599</td></tr>
<tr><td>>120 min (n=170)</td><td>4/14 (28.6%)</td><td>35/156 (22.4%)</td><td>0.601</td></tr>
</table>
</td>
</tr>
</table>

Baker[187]

Study type:

Prospective cohort study

EL:2 +

Country:

USA

Aim:

To test the hypothesis that if response to antipyretics in febrile children varies according to diagnosis.

Method, inclusion/ exclusion:

Prospectively studied the temperature response to acetaminophen of febrile children who came to an urban paediatric emergency and walk-in facility. A total of 3911 patients were seen during the study period and 47% were pre-medicated and excluded. Of the 2055 eligible patients, 76 (4%) were erroneously omitted and 420 (20%) were evaluated and discharged within 1 hour of acetaminophen treatment,

The study group consisted of 1,559 patients between the ages of 8 weeks and 6 years whose temperatures when seen were greater than 38.4 °C and who had not received antipyretic treatment within the previous four hours. Acetaminophen (15 mg/kg) was administered to each child and repeat temperatures were taken one and two hours later. Patient management was unaffected by the study, and physicians were unaware of the repeat temperature measurements.

Children with cultures positive for bacterial disease or chest x-ray films positive for pneumonia had slightly greater one- and two-hour temperature decreases compared with children with other diagnoses. Although statistically significant, the authors do not consider these differences in response to be clinically useful (see table below).

Table : One- and two-hour temperature response

Diagnosis	Initial temperature(n=1559) (Mean °C)	1- hr change(n=1559) (Mean °C)	2-hr change(n=471) (Mean °C)
Group A hemolytic Streptococcus pharyngitis	39.3±0.5	1.3±0.5*	1.4±0.4*
Bacterial disease	39.7±0.8	1.3±0.8*	1.8±0.5*
Gastroenteritis	39.5±0.6	1.1±0.6	1.4±0.7
Pneumonia	39.6±0.7	1.2±0.6*	1.8±0.6*
Viral disease	39.6±0.6	1.0±0.6	1.4±0.7*
Otitis media	39.6±0.6	1.0±0.6	1.5±0.7*
Miscellaneous	39.5±0.4	1.0±0.6	1.6±0.7*
Total	39.5±0.6	1.0±0.6	1.6±0.7*
*: p< 0.01, analysis of variance			

Table : temperature responses in children with bacterial deep tissue infections

Diagnosis (No)	Initial temp (Mean °C)	1- hr change (Mean °C)	2-hr change (Mean °C)
Sepsis (10)	40.1	1.5	1.8
Meningitis (5)	39.5	1.1	1.1
Osteomyelitis (2)	39.4	1.3	2.6

Richardson[188] study type: conference abstract EL: 4	Country: USA Aim: The hypothesis: The clinical appearance of febrile children without recent antipyrectic treatment at the time of presentation would predict serious illness. The clinical appearance of the children who initially appeared ill assessed 1 hour after receiving acetaminophen would further refine the prediction of serious illness. Method, inclusion/ exclusion Children ≤ 24 months seen in the ED with rectal temperature ≥38.3 °C and who had not had antipyretics in the previous 4 hours were enrolled. After the initial assessment using YOS, 15 mg/ kg of acetaminophen was given orally. Phone follow-up was done on day 5. serious illness was defined as : bacterial illness, significant abnormalities of electrolytes, blood gas, chest x-ray or CSF pleocytosis or illness requiring extended in-patient therapy.	195 patients were enrolled, with a mean age of 10.5 months, 17/195 (8.7%) were seriously ill. 62/195 appeared ill at presentation (YOS ≥10). 14/62 children who initially appeared ill were seriously ill. For the 62 children who initially appeared ill, 1 hour after acetaminophen the mean temperature in the seriously ill group was 38.8^{o}c compared with 38.4 °C in children without serious illness (not significant, p value not reported). The mean repeat YOS was 13.7 in children with serious illness compared with 10.0 in the children without serious illness (p=0.004). The authors concluded that children with serious illness generally appear more ill than those without before and after acetaminophen.

Evidence table of likely bacterial causes of serious bacterial infections in the UK after 1992.

<table>
<tr><th>Citation/ EL</th><th>Method</th><th>Results</th></tr>
<tr><td>Nademi[121]

<u>Study type:</u>
Prospective cohort study
EL: 2+</td><td>All children presenting to hospital with temperatures ≥38 °C see in two hospitals in New Castle between August to October 1999.</td><td>
One hundred and forty one children between 8 days and 16 years of age were studied, 64% male, 55% aged under 2 years. Serious disease was present in 41 (29%) with 31 (22%) microbiologically or radiologically proven and the other 10 given a diagnosis of sepsis cause including three patients with clinical signs of meningococcal disease but without any positive culture.

35/41 (86%) of patients with serious bacterial infections had temperatures between 38 and 39 °C and 3 (7%) had temperature between 38-39 °C. Ninety six percent were casualty or GP referrals and 4% were tertiary referrals. Twenty nine percent (41/141) had serious disease but microbiologically or radiologically proven in only 22% (31/141); pneumonia (nine), meningitis (seven), sepsis (five), urinary tract infection (five), brain abscess (two), toxic shock syndrome (one), appendicitis (one), ischiorectal abscess (one). Forty two percent (5/12) of microbiologically proven meningitis and sepsis and 36% (8/22) of all meningitis and sepsis were meningococcal. 71% had non-serious diseases. In cases of serious disease the temperature was >39 °C in 15% (sensitivity: 14%, specificity: 82%, PPV: 25%). Poor feeding and restlessness predicted serious disease with a sensitivity of 78% and 76%, respectively. Full blood count (FBC) was taken in 50% of patients on admission; in 44% of serious and 24% of non-serious diseases WBC was between 5000 and 15 000/mm^3 and WBC ≥15 000/mm^3 was seen in 39% of serious diseases (sensitivity:10%, specificity: 95%, PPV: 44%).

BT > 39 °C had sensitivity of 14% (3-25%), specificity 82% (74-89%), PPV 25% (7-42%) and NPV (70 61-78%).

Definition of serious infections: sepsis, meningitis, toxic shock syndrome, brain abscess, pneumonia, UTI, ischiorectal abscess, appendicitis.

Table : Lab investigations
<table>
<tr><th></th><th>No. of patients</th><th>No of positive results</th><th>Details</th></tr>
<tr><td>Blood culture</td><td>59</td><td>6</td><td>N. meningitidis (3)
S. pneumoniae (2)
H. influenzae (1)</td></tr>
<tr><td>Lumbar puncture</td><td>17</td><td>7</td><td>S. pneumoniae (2)
S. epidermidis (1)
H. influenzae (1)
N. meningitidis GB (1)
Pos CSF profile (1)
Enterovirus (PCR) (1)</td></tr>
<tr><td>Urine microscopy</td><td>99</td><td>10</td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/ EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Throat swab</td><td>29</td><td>12</td><td>HSV1 (4)
βH streptococci GA (2)
RSV (2)
S. aureus (1)
S. pneumoniae (1)
H. influenzae (1)
Pseudomonas (1)</td></tr>
<tr><td>Blood serology</td><td>12</td><td>1</td><td>Anti-streptolysin O=500</td></tr>
<tr><td>PCR</td><td>11</td><td>3</td><td>N. meningitidis (2)
Enterovirus (1)</td></tr>
</table>
</td></tr>
<tr><td>Osman[201]

<u>Study type:</u>
Prospective cohort study
EL: 2+</td><td>This is an observational prospective study done at the Accident and Emergency Department of the Royal Hospital for Sick Children, Edinburgh where approximately 30,000 patients under the age of fourteen are seen annually. The study period was chosen to coincide with the peak incidence of infectious diseases. Between 10 Dec. 1997 and 22 Feb. 1998, data were collected prospectively for all children presenting with an infectious illness. These were identified by the diagnosis made by the attending doctor, or else defined as symptoms suggestive of an infectious process, either specific e.g. cough or general such as fever or being unwell in the absence of a history of trauma or toxic ingestion. An experienced nurse recorded</td><td>A total of 5021 patients, including surgical patients, were seen during the nine week period with 1547 (31%) patients presenting with features of an infectious illness. Hereafter, the discussion concerns only this latter group. The median age was 17 months (range 0.1-224). There were 804 (52%) males and 743 (48%) females. Forty six per cent of the patients were self-referred and 45% were referred by their general practitioners. The remainder were from other sources, such as school nurses. The mean temperature for all the patients was 37.5ºC (SD 1.1, range 34.8-40.6) with 42% of the patients being febrile on presentation (axillary temperature ≥37.5ºC) and 22% with a temperature ≥38.5ºC.

Hospitalisation. The admission rate for the studied group was 41% (635/1547) Admitted children were younger and had a significantly higher temperature than these who were not admitted (both p=0.0005). More children were admitted when referred by their GPs than if they self-referred (p=0.0005). In only 133 (21%) of cases was the reason for admission stated. The height of temperature was indicated as a reason for admission in 20% patients. In 11% of admissions parental anxiety or request were mentioned among the reasons for admission and a further 3% were for other social reasons. Uncertain diagnosis accounted for 10% of admissions, whereas in the majority of patients the severity of illness was identified as the reason for admission. The median duration of hospital stay was 2.7 days, with a range of 1 to 31 days.

Need for hospital treatment. Only 44% of the admitted patients had some form of treatment necessitating hospitalisation. The source of referral did not indicate the need for hospital treatment (χ^2 0.484 df1, p=0.487), and there was no difference in length of hospital stay between GP and self-referred patients (p=0.547 MW test). Among many clinical and laboratory parameters evaluated, only the illness severity score predicted the need for hospital treatment.

Type of infection. The temperature was significantly higher in bacterial infections (p = 0.006). Less than 20% of patients with non-bacterial infections had a temperature greater than 38.5ºC. However, the positive predictive value of fever of this magnitude in predicting bacterial infection was only 40%. At a cut-off value of $10x10^9/1$, the absolute neutrophil count had a sensitivity and specificity of 54% and 72% respectively, for predicting bacterial infection (with 47% and 77% positive and negative predictive</td></tr>
</table>

<table>
<tr><th>Citation/ EL</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>vital signs, including axillary temperature, for all patients. Doctors attending those children recorded the provisional diagnosis on a study pro forma, on which detailed clinical and laboratory data were then collected.</td><td>values respectively). The corresponding values for the white cell count were almost the same as those of the neutrophil count. Only the absolute neutrophil count and the possibility score retained significance in a regression model for the prediction of bacterial infection.

Blood culture. Blood was obtained for culture from 275 (43%) of the 635 patients admitted. Patients who were investigated with a blood culture were older than those who were not (median age 34.1m and 29.6m respectively, p=0.001). At higher temperatures, more patients were investigated with blood culture and more had bacteraemic illness (χ^2 20.4, df2. p=0.0001, Kruskal-Wallis test). Seven (2.5%) blood cultures were positive for pathogenic organisms (SE: 0.0095, CI: 0.007 - 0.044). It is noteworthy that none of the three patients with clinically diagnosed and treated meningococcal septicaemia had a positive blood culture. A throat swab from one of these patients grew Neisseria meningitidis. The absence of Haemophilus influenzae type b was also evident.

Antecedent antibiotic treatment did not influence culture results (χ^2 0.517, df=l, p=0.680, Fisher exact test). However, the small number of patients in the positive group limits the strength of this comparison. Bacteraemic patients had significantly higher temperatures (p=0.0372) and higher neutrophil (p=0.0056) and total white cell counts (p=0.0135). The sensitivity and specificity of temperature >38.5ºC in predicting a positive blood culture were 71% and 63% respectively (PPV 5%, NPV 99%). The figures for neutrophilia as defined above were comparable to those of high fever. On logistic regression, only temperature remained a sole independent predictor of bacteraemia. It was notable that only a very small number (10%) of patients evaluated by a blood culture had either CRP or ESR done.

Table. Details of the positive blood cultures
<table>
<tr><td>Organism</td><td>number</td></tr>
<tr><td>Haemophilus influenzae biotype V noncapsulated</td><td>1</td></tr>
<tr><td>Group B beta haemolytic streptococcus</td><td>1</td></tr>
<tr><td>Streptococcus pneumoniae group 6</td><td>2</td></tr>
<tr><td>Streptococcus pneumoniae group 23</td><td>1</td></tr>
<tr><td>Streptococcus pneumoniae group 14a</td><td>1</td></tr>
<tr><td>E. coli (coliforms)</td><td>1</td></tr>
<tr><td>Total</td><td>7</td></tr>
</table></td></tr>
<tr><td>Laundy[202]

<u>Study type:</u>
Prospective cohort study</td><td>6-month prospective study of paediatric accident and emergency and general practice consultations with a diagnosis of community-acquired pneumonia (CAP).

Population:</td><td>Nasopharyngeal aspirates for viral immunofluorescence and PCR studies and blood cultures for bacterial studies were taken from 51 (age ranged from 2 weeks to 4.8 years, median age of 1.3 years; 63% girl) children with symptoms, signs and chest radiographic features that satisfied a diagnosis of pneumonia.

45 patients (88%) were recruited from the hospital emergency department and 6 from GP. 42 (82%) were hospitalised.

An etiologic agent was isolated from 25 patients (49%). A viral cause was identified in 22 patients (43%), and influenza A virus and respiratory syncytial virus (RSV) were detected in 16 and 18% of all cases, respectively. Moreover, they found 1 case (2%)</td></tr>
</table>

Citation/ EL	Method	Results
EL: 2+	The study population was from the catchments area for Royal London Hospital, East London from 30/09/2001-30/03/2002. Any child younger than 5 years with symptoms and signs indicating CAP was eligible regardless of risk factors. VAP was defined as a respiratory illness with fever >38.5OC and tachypnoea (respiratory rate > 40/min in children 1-5 years; >50/min for 1-11 months and >60/min < 1 months) with or without cough, plus evidence of consolidation from clinical exam or chest radiography. Children with fever who were not tachypnoeic but had clinical evidence of consolidation on chest radiogram were included. Exclusion: young children with obvious bronchiolitis were excluded.	with enterovirus, 3 cases (6%) with parainfluenza, 3 with adenovirus (6%). Only four patients (8%) had a positive bacterial blood culture; three had Streptococcus pneumoniae and one had Neisseria meningitidis W135. Mycoplasma pneumoniae was detected in 2 children, and mixed infections were detected in 5 (10%). The use of viral PCR increased the detection rate of influenza A virus by 100%.
Richardson[203] <u>Study type:</u> Prospective cohort study EL: 2+	This is a multicentre prospective study including 21 hospitals in the south and west of England and South Wales between November 1993 to April 1995. 124 (83% of eligible population) children between the ages of 4 weeks and 16 years with newly diagnosed bacterial meningitis. The age ranged 0.1-15.6 years (median 2.1 years) with no fatality in this series.	Ninety two children (74%) had meningococcal and 18 (15%) had pneumococcal meningitis. Fifty two of these children had *Neisseria meningitidis* isolated by microscopy or culture of cerebrospinal fluid. Twenty six patients had cerebrospinal fluid pleocytosis plus positive meningococcal blood cultures or petechiae, and 14 children who did not undergo lumbar puncture had meningism and evidence of meningococcal disease. *Streptococcus pneumoniae* was isolated from the cerebrospinal fluid of 18 patients (15%). There was one case each of meningitis due to *Haemophilus influenzae* type b, *Listeria monocytogenes*, and group B streptococcus. In the remaining 11 cases (8%), all of whom had a cerebrospinal fluid neutrophil pleocytosis, the pathogen was unknown. Thirty four children had received parenteral penicillin before admission. This included 24 of the 26 patients with cerebrospinal fluid pleocytosis and signs of meningococcal disease.
Palmer[281]	During 1998, each case of meningococcal disease reported by	In Wales, in 1998, 119 (63 male) patients with meningococcal were identified.

<table>
<tr><th>Citation/ EL</th><th>Method</th><th>Results</th></tr>
<tr><td><u>Study type:</u>
Prospective cohort study
EL: 2+</td><td>all Medical Officers for Environment Health in Wales, the information resource included GP, hospital clinicians and microbiologists. Patients were identified from statutory notifications, reports from data provided by Manchester Public Health Lab (PHL). Meningococcal Reference Lab. Patients with clinical features of meningitis but whose diagnosis was not confirmed by blood or CSF culture, were considered to have meningococcal disease when a purpuric rush and an abnormal CSF were reported.</td><td>They included 10 without an organism cultured from blood or CSF and without evidence of purpuric rash. In five of those 10, diplococci were seen in the CSF; in the other five, the CSF was abnormal. The crude incidence, in 1998, in Wales was 4.2 cases/ 100 000. The age specific incidence was 83/ 100 000 in infants, 35/100 000 in 1-4 year-old, 5/100 000 in 5-14 year-old and 1/100 000 in adults. The peak incidence was between January and April, with a smaller peak towards the end of the year. The fatality rate was 3% (1/31) in infants, 10% (5/51) in 1-4 year-old, 18% (3/17) in 5-14 year-old and 20%(4/20) in older teenagers and adults.

Microbiology

Among 105 of the 111 meningococcal strains identified at Manchester PHL, there were 77 group B strains (74% sulphonamide sensitive), 27 group C strain (63% sulphonamide sensitive) and 1 group Y strain (sulphonamide sensitive). There were 26 different serotypes, the most common being B2bnt (n: 23), $B_1$5P1.16 (n: 12), Bnt nt (n: 11), Bnt P1.15 (n: 11) and Cnt nt (n: 9).

Clinical features:

Signs and symptoms reported in cases of meningococcal disease
<table>
<tr><th></th><th><1 year (n=25)</th><th>1-4 year (n=39)</th><th>5-14 year (n=13)</th></tr>
<tr><td>Fever</td><td>20 (80%)</td><td>35 (90%)</td><td>11 (85%)</td></tr>
<tr><td>Vomiting</td><td>14 (56%)</td><td>31 (79%)</td><td>11 (85%)</td></tr>
<tr><td>Fever & vomiting</td><td>13 (52%)</td><td>28 (72%)</td><td>8 (62%)</td></tr>
<tr><td>Refusal of feeds</td><td>16 (64%)</td><td>15 (38%)</td><td>-</td></tr>
<tr><td>Loss of appetite</td><td>-</td><td>18 (46%)</td><td>5 (38%)</td></tr>
<tr><td>Listless</td><td>13 (52%)</td><td>27 (69%)</td><td>5 (38%)</td></tr>
<tr><td>Floppy</td><td>5 (20%)</td><td>12 (31%)</td><td>1 (8%)</td></tr>
<tr><td>Pallor</td><td>8 (32%)</td><td>12(31%)</td><td>6(46%)</td></tr>
<tr><td>Photophobia</td><td>3 (12%)</td><td>3 (8%)</td><td>2(15%)</td></tr>
<tr><td>Headache</td><td>-</td><td>10(26%)</td><td>9(69%)</td></tr>
<tr><td>Neck stiffness</td><td>5(20%)</td><td>19 (49%)</td><td>5(38%)</td></tr>
<tr><td>Rash</td><td>19 (76%)</td><td>35 (90%)</td><td>11(85%)</td></tr>
</table>
</td></tr>
</table>

Citation/ EL	Method	Results

purpuric rash other rash	13 (52%) 6(24%)	32(82%) 3(8%)	9(69%) 2(15%)
Fever, vomiting and rash	9(36%)	24(62%)	5(38%)
Neck stiffness and rash	3(12%)	17(44%)	5(38%)
Neck stiffness or rash	21(84%)	37(95%)	12(92%)
Neck stiffness, rash and headache	1 (4%)	5(13%)	4(31%)
Neck stiffness, vomiting and headache	4(16%)	12(31%)	5(38%)
Convulsions	3(12%)	6(15%)	1(8%)
Coma	1(4%)	3(8%)	1(8%)
Shock	3(12%)	8(21%)	-

Physical methods

<table>
<tr><th>Citation/ El</th><th>Method</th><th>Results</th></tr>
<tr><td>Axelrod[208]

Study Type: Review.
Evidence level: 1+</td><td>Number of People: 2 large RCT

RCT comparing the use of tepid sponge bath with antipyretics alone for young children with temp ≥38.9 °C</td><td>The use of tepid sponge bath with antipyretics alone for young children with temp ≥38.9 °C demonstrated unequivocal superiority of drugs for reduction of BT within 2-3 hours of initial treatment. Physical cooling methods are clearly indicated for the treatment of hyperthermia, but their use for the treatment of fever remains controversial because of their propensity to induce cutaneous vasoconstriction.

Drugs tended to work more slowly than tepid sponging.

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td colspan="2">Cooling</td><td></td></tr>
<tr><td>Reference</td><td>N</td><td>Age, y</td><td>Initial temp (°C)</td><td>Antipyretic drug</td><td>First 30 min</td><td>Overall</td><td>Increased discomfort</td></tr>
<tr><td>Aksoylar[282]</td><td>224</td><td>0.5-5</td><td>RT≥39</td><td>As, P, I</td><td>Best with sponging</td><td>Best with drug (3°c different at 3 h)</td><td>Not ascertained</td></tr>
<tr><td>Agbolasu[283]</td><td>80</td><td>0.5-4.5</td><td>AT39.5-40</td><td>P</td><td>Sponging equivalent</td><td>Best with drug (1.5°c different at 2 h)</td><td>No (qualitative)</td></tr>
</table>

Studies in randomised studies: comparisons of the use of sponging plus administration of drugs with drugs alone.

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td colspan="2">Cooling</td><td></td></tr>
<tr><td>Reference</td><td>N</td><td>Age, y</td><td>Initial temp (°C)</td><td>Antipyretic drug</td><td>First 30 min</td><td>Overall</td><td>Increased discomfort</td></tr>
<tr><td>32</td><td>115</td><td>0.5-5</td><td>≥39.4</td><td>A</td><td>Combination superior</td><td>Combination superior:
Sponging with ice water or alc & H_2O superior to sponging to tepid water</td><td>Sponging with ice water or alc & H_2O was more uncomfortable</td></tr>
<tr><td>33</td><td>37</td><td>0.5-5</td><td>≥39.</td><td>As, P</td><td>No difference</td><td>No difference</td><td>No</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/ EI</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td></td><td></td><td>5</td><td></td><td></td><td></td><td></td></tr>
<tr><td>34</td><td>130</td><td>0.25-2</td><td>≥39.0</td><td>As, A</td><td>No difference at 50 min</td><td>No difference</td><td>7 children were removed from the study due to shivering.</td></tr>
<tr><td>35</td><td>54</td><td>0.33-4</td><td>≥38.9</td><td>A</td><td>No difference</td><td>Combination superior at 60 min</td><td>No</td></tr>
<tr><td>36</td><td>26</td><td>0.5-5</td><td>≥38.5</td><td>P</td><td>Combine superior</td><td>Combination superior over 4 h, small difference</td><td>Yes: by parent assessment</td></tr>
<tr><td>37</td><td>75</td><td>0.5-5</td><td>≥38.5</td><td>P</td><td>Combination superior</td><td>Combination superior for time to reach temp < 38C; 10% have fever rebound in combination group 0% in drug group.</td><td>Yes: mainly crying; 1 child shivered.</td></tr>
<tr><td>38</td><td>20</td><td>0.5-6</td><td>≥38.9</td><td>A</td><td>Combination superior, 1st hour</td><td>No difference</td><td>yes</td></tr>
</table>
A: Acetaminophen
P: Paracetamol
I: Ibuprofen
As: Aspirin
</td></tr>
<tr><td>Purssell[209]

<u>Study Type:</u></td><td>Number of People: Included 4 studies The effect of tepid sponging alongside with paracetamol s. Outcome Measures:

Temp reduction, adverse events</td><td>The effectiveness of tepid sponging as a treatment alongside paracetamol varies between studies, two studies found them helpful, two studies found it is of no benefit.

However, even when a positive effect is seen with the addition of sponging to paracetamol, the difference in temperature reduction between those receiving the sponging is small: at one hour, the mean difference in temperature reduction of the three studies reporting this figure was 0.4 °C.</td></tr>
</table>

<table>
<tr><th>Citation/ El</th><th>Method</th><th>Results</th></tr>
<tr><td>review. EL: 2+</td><td></td><td>Side effects and tolerability

3 studies reported shivering, and mention of crying.

One study reported pronounced discomfort in one patient receiving sponging, but crying was reported in over half of this group compared with less than 1/10 in the paracetamol group, another study noted that equal numbers of children objected to, and enjoyed the sponging... The addition of tepid sponging to paracetamol in the treatment of children offers little advantages over the administration of paracetamol alone in most cases Although it might result in a slightly faster fall in temp, this benefit is short lasting.
<table>
<tr><td>Paracetamol dose</td><td>Water temp</td><td>Sponging time</td><td>Temp difference</td></tr>
<tr><td>5-10 mg/ kg</td><td>Neutral</td><td>20 min</td><td>0.2 °C</td></tr>
<tr><td>15 mg/kg</td><td>31.1 °C</td><td>15 min</td><td>0.8 °C</td></tr>
<tr><td>120 mg (< 1yr)</td><td></td><td></td><td></td></tr>
<tr><td>240 mg (> 1yr)</td><td>< BT</td><td>10-20 min</td><td>0.1 °C</td></tr>
<tr><td>10-15 mg/kg</td><td>29-30 °C</td><td>Until <38 °C</td><td>Not reported</td></tr>
</table></td></tr>
<tr><td>Meremikwu[213]

Study Type: SR. EL: 1++</td><td>Aim:

To evaluate the benefits and harms of physical cooling methods used for managing fever in children.

Method:

They searched the Cochrane Infectious Diseases Group's trials register (February 2003), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1, 2003), MEDLINE (1966 to February 2003), EMBASE (1988 to November 2002), LILACS (February 2003), CINAHL (1982 to February</td><td>. One small trial (n = 30), comparing physical methods with drug placebo, did not demonstrate a difference in the proportion of children without fever by one hour after treatment in a comparison between physical methods alone and drug placebo. In two studies, where all children received an antipyretic drug, physical methods resulted in a higher proportion of children without fever at one hour (n = 125; relative risk 11.76; 95% confidence interval 3.39 to 40.79). In a third study (n = 130), which only reported mean change in temperature, no difference was detected. Mild adverse events (shivering and goose pimples) were more common in the physical methods group (3 trials; relative risk 5.09; 95% confidence interval 1.56 to 16.60). Conclusions: A few small studies demonstrate that tepid sponging helps to reduce fever in children Background: Health workers recommend bathing, sponging, and other physical methods to treat fever in children and to avoid febrile convulsions. We know little about the most effective methods or how these methods compare with commonly used drugs. Objectives: To evaluate the benefits and harms of physical cooling methods used for managing fever in children. Search strategy: We searched the Cochrane Infectious Diseases Group's trials register (February 2003), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 1, 2003), MEDLINE (1966 to February 2003), EMBASE (1988 to November 2002), LILACS (February 2003), CINAHL (1982 to February 2003), Science Citation Index (1981 to February 2003), and reference lists of articles. We also contacted researchers in the field. Selection criteria: Randomized and quasi-randomized controlled trials comparing physical methods with a drug placebo or no treatment in children with fever of presumed infectious origin. We included studies where children in both groups were given an</td></tr>
</table>

Citation/ EI	Method	Results
	2003), Science Citation Index (1981 to February 2003), and reference lists of articles. We also contacted researchers in the field. Selection criteria: Randomized and quasi-randomized controlled trials comparing physical methods with a drug placebo or no treatment in children with fever of presumed infectious origin. We included studies where children in both groups were given an antipyretic drug. Data collection and analysis: Two reviewers independently assessed trial methodological quality. One reviewer extracted data and the other checked the data for accuracy. Results were expressed as relative risk with 95% confidence intervals for binary outcomes, and weighted mean difference for continuous data. Main results: Seven trials, involving 467 participants, met the inclusion criteria	antipyretic drug. Data collection and analysis: Two reviewers independently assessed trial methodological quality. One reviewer extracted data and the other checked the data for accuracy. Results were expressed as relative risk with 95% confidence intervals for binary outcomes, and weighted mean difference for continuous data. Main results: Seven trials, involving 467 participants, met the inclusion criteria. One small trial (n = 30), comparing physical methods with drug placebo, did not demonstrate a difference in the proportion of children without fever by one hour after treatment in a comparison between physical methods alone and drug placebo. In two studies, where all children received an antipyretic drug, physical methods resulted in a higher proportion of children without fever at one hour (n = 125; relative risk 11.76; 95% confidence interval 3.39 to 40.79). In a third study (n = 130), which only reported mean change in temperature, no difference was detected. Mild adverse events (shivering and goose pimples) were more common in the physical methods group (3 trials; relative risk 5.09; 95% confidence interval 1.56 to 16.60). Conclusions: A few small studies demonstrate that tepid sponging helps to reduce fever in children

Drug interventions

<table>
<tr><th>Citation/ EI</th><th>Method</th><th>Results</th></tr>
<tr><td>Purssell[214]

Study Type: Review.
EL: 1+</td><td>Inclusion: Primary studies comparing oral paracetamol and ibuprofen as treatments for fever in children, and included sufficient statistics to extract mean temp and effect size at either or all of 0,1,2,4, and 6 hr. oral paracetamol and ibuprofen as treatments for fever in children,</td><td>The author found 13 papers and 8 were included. 5 of them used randomization. The age studied ranged from 4 mo to 13 yr.

Differences in temp between ibuprofen and paracetamol
<table>
<tr><th>T</th><th>M. diff (^{O}C)</th><th>95%CI</th><th>No.</th><th>p</th></tr>
<tr><td>1 hr</td><td>-0.01</td><td>-0.04 :0.02</td><td>5 s
n:448</td><td>0.22</td></tr>
<tr><td>4 hr</td><td>0.63</td><td>0.59: 0.69</td><td>6 s
n:423</td><td><0.00 1</td></tr>
<tr><td>6 hr</td><td>0.58</td><td>0.52: 0.64</td><td>5s
n:267</td><td>0.005</td></tr>
</table>
T: time; S: studies

The differences that exist appear to be unrelated to dosages of the drugs. This is further supported by the high degree of homogeneity across drug dosages at 4 and 6 hr.

Data extraction was done by one person and the potential for bias or error in extraction and interpretation exists.

Lack of uniformity about the dosage of drugs.

Overall, it appears that ibuprofen is more effective than paracetamol, particularly at 4 and 6 hr.</td></tr>
<tr><td>Perrott[210]

Study Type: SR.
EL: 1+</td><td>Number of People: Seventeen blinded, randomized controlled trials with 915 children (<18 years). Inclusion/exclusion: children (<18 years) receiving either drug to treat fever or moderate to severe pain. Single-dose acetaminophen and ibuprofen for treating children's pain or fever.</td><td>Under a fixed-effects model, outcome measures for an initial single dose of ibuprofen vs. acetaminophen were the risk ratio for achieving more than 50% of maximum pain relief, effect size for febrile temperature reduction, and risk ratio for minor and major harm. Data Synthesis: Ibuprofen (4-10 mg/kg) and acetaminophen (7-15 mg/kg) showed comparable efficacy (3 pain relief trials; 186 children). The risk ratio point-estimates was 1.14 (95%confidence interval [CI], 0.82-1.58) at 2 hours after receiving the dose, and 1.11 (95% CI, 0.89-1.38) at 4 hours. Ibuprofen (5-10 mg/kg) reduced temperature more than acetaminophen (10-15 mg/kg) at 2, 4, and 6 hours after treatment (respective weighted-effect sizes: 0.19 [95% CI, 0.05-0.33], 0.31 [95% CI, 0.19-0.44], and 0.33 [95% CI, 0.19-0.47]) (9 fever trials; 1078 children). For ibuprofen 10 mg/kg (acetaminophen, 10-15 mg/kg), corresponding effect sizes were 0.34 (95% CI, 0.12-0.56), 0.81 (95% CI, 0.56-1.03), and 0.66 (95% CI, 0.44-0.87). There was no evidence the drugs cause serious harm.</td></tr>
</table>

<table>
<tr><th>Citation/ El</th><th>Method</th><th>Results</th></tr>
<tr><td>Wong[215]

<u>Study Type:</u> RCT
EL: 1+</td><td>Multiracial, multinational, multicentre, single, oral dose, prospective, randomised, modified parallel group study.

Ibuprofen vs. Acetaminophen vs. Dipyrone. Number of People: 555 patients completed the study 179 in the dipyrone group191 in the acetaminophen group and 185 in the ibuprofen group... Inclusion/exclusion: Approached 628 febrile children, 6 mo to 6 yr with body weight ≥5 kg and able to receive oral medication. Recruited from May to December 1998. They were identified either in inpatient ward or emergency clinics. Exclusion:

Having history of febrile seizures within 6 mo prior to the study, receiving Abx more than 12 hr before study, receiving antipyretics with 4 hr of study, receiving treatment with any investigational drug in the prior 4 weeks, and having a history of hypersensitivity or adverse reaction of the study drugs.

Children were also excluded if they had poor prognosis (tropical disease e.g. dengue fever, malaria, fever, cramps, and/or severe dehydration. Conditions that might interfere with drug absorption; histories of connective tissue disease or AIDS; haematological toxic effects within the past 3 mo; changes in mood or conscious.

Outcome Measures: Definition of fever:</td><td>All three drugs were effective in reducing TT. Time reach this reduction was statistically comparable for all three groups.

The number of pt who achieved normalisation was significantly greater in the dipyrone and ibuprofen group than in the acetaminophen group (p=0.004).

Temperature reductions of at least until the end of 6 hr observation only with dipyrone. Reductions in a similar range were maintained with acetaminophen and ibuprofen for up to 3 hr.

Absolute reduction of temp over time: similar during the first 2 hr. At 4-5-6 hr, mean temp in dipyrone is significantly lower (p=0.004).

Tolerability:

Drug related adverse effects: 17% in dipyrone; 15% in acetaminophen and 27 in ibuprofen (ns, p value not reported).

BP and pulse rate tended to decrease uniformly.

Total of 9 pt (3 in the dipyrone; 2 in acetaminophen and 4 in ibuprofen) had temp < 36.0 °C.

During the study periods, anticonvulsants, antacids, corticosteroids, or non-steroidal anti-inflammatory drugs were prohibited.

Baseline characteristics
<table>
<tr><th></th><th>Dipyrone (n=209)</th><th>Acetaminophen (n=210)</th><th>Ibuprofen (n=209)</th></tr>
<tr><td>Age (mo)
Mean ±SD
Range</td><td>
28±18
6-80</td><td>
31±21
6-91</td><td>
29±19
6-83</td></tr>
<tr><td>Weight
Mean ±SD
Range</td><td>
13±4
6-26</td><td>
13±5
6-30</td><td>
13±4
6-28</td></tr>
<tr><td>TT (°C)</td><td>39.3±0.6</td><td>39.2±0.6</td><td>39.2±0.6</td></tr>
<tr><td>Diagnosis
URI</td><td>
135 (64%)</td><td>
145 (69%)</td><td>
134 (64%)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/ EI</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>TT 38.5-40.5 °C.

TT of the right ear were obtained by a digital otoscopic temperature device (Thermoscan HM2W/C; Braun, Inc). In children < 3yr, 3 successive readings were taken, and the highest temp was recorded.

Patients were randomly assigned 1:1:1 to receive one of the drugs in a single dose by syringe. The dosage and manner of administration per manufacturers' labelling instructions in the packaging insert, exactly as the caregiver would do in the domestic situation.

The dosage of dipyrone (Novalgina) was 15 mg/ kg. the dose for acetaminophen (Tylenol) was adjusted according to each pt's age, averaged 12 mg/kg. Ibuprofen (Ibupirac) was given in initial temperature using dose of 5 mg/ kg for <39.2 °C and 10 mg/kg for ≥39.2 °C.

Evaluation:

After medication, TT was measured 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, and 6 hours later.

Adverse events were assessed during the 6 hr study period and for an additional 14 days after drug ingestion.</td><td>
<table>
<tr><td>LRI</td><td>37 (18%)</td><td>44 (21%)</td><td>40 (19%)</td></tr>
<tr><td>UTI</td><td>6 (3%)</td><td>1 (0.5%)</td><td>10 (5%)</td></tr>
<tr><td>GI infection</td><td>26 (12%)</td><td>25 (12%)</td><td>26 (12%)</td></tr>
<tr><td>Other</td><td>44 (21%)</td><td>37 (18%)</td><td>39 (19%)</td></tr>
</table>

Temperature reduction:

<table>
<tr><td></td><td>Dipyrone (n=179)</td><td>Acetaminophen (n=191)</td><td>Ibuprofen (n=185)</td></tr>
<tr><td>Pt (N[%]) with TT reduction ≥ 1.5 °C</td><td>154 (86)</td><td>148 (77)</td><td>153 (83)</td></tr>
<tr><td>Time to temp reduction
Mean (min ±SD)
Range</td><td>
103±68
15-360</td><td>
109±77
15-360</td><td>
120±83
15-360</td></tr>
<tr><td>Pt (N[%]) with normalised temp (TT≤37.5 °C)</td><td>147(82)</td><td>130 (68)</td><td>145 (78)</td></tr>
<tr><td>Time to temperature normalisation
Mean (min ±SD)
Range</td><td>

123±71
15-360</td><td>

118±80
15-360</td><td>

130±87
15-360</td></tr>
</table>
</td></tr>
<tr><td>Figueras[216]</td><td>Number of People: Population: 6 mo- 12 yr.

A total of 200 paediatric inpatients were</td><td>Efficacy:

The evolution of temp over time was not significantly different between ibuprofen and paracetamol groups (p=0.22).</td></tr>
</table>

<table>
<tr><th>Citation/ EI</th><th>Method</th><th>Results</th></tr>
<tr><td>Study Type: RCT
EL: 1+</td><td>randomly allocated to either intervention or control group.

Inclusion/exclusion: Age (Y): Mean (SD) 3.48 (2.7) in the ibuprofen and 3.78 (3.0) paracetamol.

Inclusion:

Body weigh > 3rd centile and absence of CNS infection symptoms, bilateral otitis or any other condition which the investigator’s judgment would make it inadvisable for the enrolment.

Exclusion:

Had history of malabsorption, febrile crisis over the past 6 mo, hypersensitivity to NASIDs or paracetamol, GI bleeding, significant renal, hepatic, pulmonary, endocrine, haematological, cardiac, neurological or CNS dysfunction. Uncontrolled DM, clotting alterations, or current diagnosis of epilepsy.

Had been treated with t1/2>12 h Abx within 24 hr admission. A min 4-hr washout period was mandatory before inclusion for pt who had received antipyretics within 4 hr.

A period of 6 h should have elapsed for those who had been given non-betalactamic Abx 6 hr.

Intervention: 1 drop of ibuprofen-arginine kg/ body weight (6.67 ibuprofen mg/kg) or 4 drops of paracetamol (10.65mg/kg) together with a matching placebo.

Temperature measurement:</td><td>The reduction of TT between both treatments did not differ significantly at the 4-hr control (p=0.527), with a mean decrease difference in ibuprofen group of 1.3 °C (SD 1.1) against 1.2 °C (0.96) in the paracetamol group. This reduction did not reach significance over the study period (p=0.697). The percentage reduction calculated at the 4-h point was not statistically significant between groups (65.9% for ibuprofen and 66.8% for paracetamol, p=0.96). Other antipyretic analyses such as max decrease in TT, percentage of pt with reductions in TT equal or superior to 1.5 °C were similar between groups with a better trend of ibuprofen group without reaching statistical significance. Only the percentage of pt that achieved a reduction in TT of 2 °C or more was higher in the ibuprofen group compared with the paracetamol group (22.1% against 15.6%, p=0.043) following multi-variant analysis.

<table>
<tr><td>Characteristics</td><td></td><td>Ibuprofen (n=100)</td><td>Paracetamol (n=99)</td><td>p-value</td></tr>
<tr><td>Age (Y)</td><td>Mean (SD)</td><td>3.48 (2.7)</td><td>3.78 (3.0)</td><td>0.451</td></tr>
<tr><td>Weight (kg)</td><td>Mean (SD)</td><td>16.59 (8.14)</td><td>18.59 (11.32)</td><td>0.798</td></tr>
<tr><td>Diagnosis at admission</td><td>N</td><td></td><td></td><td></td></tr>
<tr><td>URI</td><td></td><td>41</td><td>50</td><td>ns</td></tr>
<tr><td>LRI</td><td></td><td>12</td><td>16</td><td>ns</td></tr>
<tr><td>GI infection</td><td></td><td>9</td><td>3</td><td>ns</td></tr>
<tr><td>Soft tissue infection</td><td></td><td>5</td><td>7</td><td>ns</td></tr>
<tr><td>Otitis</td><td></td><td>1</td><td>0</td><td>ns</td></tr>
<tr><td>Other</td><td></td><td>25</td><td>20</td><td>ns</td></tr>
<tr><td>TT</td><td>Mean (SD) °C</td><td>39.14 (0.6)</td><td>39.13 (0.56)</td><td>0.743</td></tr>
</table>

Antipyretic activity

<table>
<tr><td>Characteristics</td><td></td><td>Ibuprofen (n=94)</td><td>Paracetamol (n=93)</td><td>p-value</td></tr>
<tr><td>Mean change in TT at 4 hr (°C)</td><td>Mean (SD)</td><td>1.3 (1.1)</td><td>120 (0.96)</td><td>0.527</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Citation/ EI</th><th>Method</th><th>Results</th></tr>
<tr><td></td><td>Fever was defined as 38.5 °C the max normal TT measured by “Thermo Scan Pro I Braun Instant Thermometer” in the oral mode”.

After administration, TT were taken at 20, 40 min, 1, 1.5,2,3,4,5,6, and 8 hr. Adverse events were assessed.</td><td>
<table>
<tr><td>Reduction of TT at 4 hr (°C)</td><td>Mean (SD)</td><td>65.9(53.9)</td><td>66.81(50.2)</td><td>0.96</td></tr>
<tr><td>Max TT change(°C)</td><td>Mean (SD)</td><td>1.91 (0.96)</td><td>1.76 (0.89)</td><td>0.205</td></tr>
<tr><td>Time become apyrexial (min)</td><td>Mean (SD)</td><td>75.1 (5.2)</td><td>77.0(5.81)</td><td>0.515</td></tr>
<tr><td>Pt with temp reduction of ≥1.5 °C</td><td>%</td><td>33.2</td><td>28.6</td><td>0.260</td></tr>
<tr><td>Pt with temp reduction of ≥2 °C</td><td>%</td><td>22.1</td><td>15.9</td><td>0.043</td></tr>
<tr><td>Pt with reduction of temp to normal range</td><td>%</td><td>43.2</td><td>40.7</td><td>0.422</td></tr>
</table>
</td></tr>
<tr><td>Walson[217]

<u>Study Type:</u> RCT
EL: 1+</td><td>Number of People: 64 pt aged from 6 mo to 11 yr 7 mo, 15 in 3 of the ibuprofen dose groups and 16 in the acetaminophen group.
Inclusion/exclusion: 64 pt aged from 6 mo to 11 yr 7 mo, weighing 6.8-56.1 kg who had been febrile for less than 48 hr and who had initial OT or RT of 39.0 0C to 40.50C.

Patients receiving any temp relating drugs, within 6 hr before study or requiring antibiotics from 12 hr before the initial dose to 24 hr after the first dose. Pt with significant GI, renal, hepatic, cardiac, haematologic, broncho-spastic, malignant or CNS disease. Pt with vomiting, severe diarrhoea, dehydration, and pt who received investigational drugs within 1 mo of the beginning of the study. Every 6 hr, each pt had 2 liquids, one of which contained placebo and one contained active drug.</td><td>By 6 hr after initiation of drug, the mean temp decreases for ibuprofen administered in doses of 2.5 mg/kg and 5 mg/ kg were less prominent than for both 10 mg/ kg ibuprofen and acetaminophen. The differences were less obvious in the 12-hr measurement.

Mean percentage reduction of fever in the group receiving 2.5 mg/kg ibuprofen (76.0%) was significant lower than that of the group receiving 10 mg/kg ibuprofen.

In 61 of the 64 evaluable patients, treatments were effective and well tolerated during the entire study. While the rates of temperature reduction and maximal reduction of fever after administration of the initial dose were equal for patients receiving 10-mg/kg ibuprofen therapy and 15-mg/kg acetaminophen therapy, and both regimens were more effective than smaller doses of ibuprofen in reducing fever, after the second dose (and continuing to the end of the study) there were no statistically significant differences in temperature response among the treatment groups. Six children were withdrawn from</td></tr>
<tr><td>Autret[218]</td><td>Number of People: Children aged 6 mo to 5 yr with fever presumed infectious origin treated with antibiotics.</td><td>Temp evolution over time was not significantly different between two groups (p not reported). The temp reduction over the first 4 hr was significantly higher after ibuprofen (60%) than acetaminophen (45%). Both drugs were well tolerated.</td></tr>
</table>

Citation/ El	Method	Results
Study Type: RCT. EL: 1+	A double blind RCT. Fever was defined as RT≥38.0 °C measured by mercury thermometer. Intervention 7.5 mg/kg ibuprofen syrup (n=77). Control: 10 mg/ kg acetaminophen syrup (n=77). Outcome Measures: Area under reduction in temp and temp evolution over time and tolerability. RT measured at 1,2,4,6,8,12,24,36,48,60,and 72 hr after the first dose. The first dose was followed 6 hr later by the second dose regardless of the degree of degree of hyperthermia. The following doses were given at regular intervals of 6 hr if the temp was > 37.8 C, up to max of 30 mg/kg for ibuprofen and 40 mg/kg/24 hr for acetaminophen.	Children < 2y and more did not show any significant difference between treatments for any of the assessment criteria. Source of funding: All drugs were supplied by Boots Pharmaceuticals.

Evidence table of the adverse effect of ibuprofen vs. acetaminophen

Systematic review

<table>
<tr><th>Citation/EL</th><th>Method</th><th>Result</th></tr>
<tr><td>Perrott[210]

<u>Study design:</u> systematic review and meta-analyses.
EL: 1+</td><td>Objective: To summarize studies testing the efficacy and safety of single-dose acetaminophen and ibuprofen for treating children's pain or fever.

Data Sources: Reports were gathered by searching computerized databases (from their inception through May 2002) and registries, relevant journals, and bibliographies of key articles.

Data extraction:
Two independent coders were blinded to identifying information about the authors, institution of affiliation, financial support, source and year of publication until meta-analyses. Disagreements were resolved by discussion.

Study Selection: Seventeen blinded, randomized controlled trials with children (<18 years) receiving either drug to treat fever or moderate to severe pain.</td><td>Under a fixed-effects model, outcome measures for an initial single dose of ibuprofen vs. acetaminophen were the risk ratio for achieving more than 50% of maximum pain relief, effect size for febrile temperature reduction, and risk ratio for minor and major harm. Data Synthesis: Ibuprofen (4-10 mg/kg) and acetaminophen (7-15 mg/kg) showed comparable efficacy (3 pain relief trials; 186 children). The risk ratio point-estimates was 1.14 (95%confidence interval [CI], 0.82-1.58) at 2 hours after receiving the dose, and 1.11 (95% CI, 0.89-1.38) at 4 hours. Ibuprofen (5-10 mg/kg) reduced temperature more than acetaminophen (10-15 mg/kg) at 2, 4, and 6 hours after treatment (respective weighted-effect sizes: 0.19 [95% CI, 0.05-0.33], 0.31 [95% CI, 0.19-0.44], and 0.33 [95% CI, 0.19-0.47]) (9 fever trials; 1078 children). For ibuprofen 10 mg/kg (acetaminophen, 10-15 mg/kg), corresponding effect sizes were 0.34 (95% CI, 0.12-0.56), 0.81 (95% CI, 0.56-1.03), and 0.66 (95% CI, 0.44-0.87). There was no evidence the drugs differed from each other (or placebo) in incidence of minor or major harm (17 safety trials; 1820 children).

<table>
<tr><td></td><td></td><td></td><td></td><td colspan="2">Dosage, mg/ kg</td><td colspan="2">No of patients</td></tr>
<tr><td>Study no.</td><td>Model</td><td>Mean age (Y)</td><td>% girls</td><td>Acetaminophen</td><td>Ibuprofen</td><td>Acetaminophen</td><td>Ibuprofen</td></tr>
<tr><td>Pain</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>McGaw</td><td>Pain (dental)</td><td>14</td><td>62</td><td>7 [A]</td><td>4[B]</td><td>43</td><td>41</td></tr>
<tr><td>Moore</td><td>Pain (dental)</td><td>8</td><td>30</td><td>10 [A]</td><td>6 [B]</td><td>11</td><td>14</td></tr>
<tr><td>Schachtel</td><td>Pain (sore throat)</td><td>9</td><td>51</td><td>15</td><td>10</td><td>38</td><td>39</td></tr>
<tr><td>Overall</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td><td>92</td><td>94</td></tr>
<tr><td>Fever</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Kauffman</td><td>Fever (temp)</td><td>6</td><td>73</td><td>10</td><td>10</td><td>8</td><td>8</td></tr>
<tr><td>Wilson</td><td>Fever (trb)</td><td>3</td><td>NA</td><td>12.5</td><td>10</td><td>51</td><td>47</td></tr>
</table>
</td></tr>
</table>

Wong	Fever (trb)	3	46	12	5 or 10 [C]	191	185	
Walson	Fever (trb)	6	53	10	10	32	25	
Autret	Fever (temp)	2	42	10	7.5	74	77	
McIntyre	Fever (trb)	2	41	12.5	5	66	69	
Starha	Fever (temp)	5	NA	10	10	26	36	
Van Esch	Fever (temp)	2	27	10	5	36	34	
Vauzelle-Kevroedan	Fever (temp)	4	49	10	10	55	58	
Walson	Fever (trb)	6	52	15	10	16	15	
Overall	NA	NA	NA	NA	NA	539	539	
10 mg/kg ibuprofen only[D]	NA	NA	NA	NA	NA	172	174	
Safety only[E]								
Bertin	Otitis media	8	44	10	10	78	77	
Bertin	Sore throat	3	56	10	10	73	71	
Hamakainen	Migraine	11	50	15	10	88	88	
Sidler	Fever	NA	NA	10	10	21	25	
Overall	NA	NA	NA	NA	NA	905[F]	915 [F]	
(temp): fever outcome measure was between drug difference in tamp at given time point ;(trb): fever outcome was between drug difference in temp reduction from baseline.								

		A: the exact dose was 240 mg/day for children under 8 yr and 360 mg/day for children aged 8 or older. B: the exact dose was 200 mg/day. C: the exact dose was 5 mg/kg if the initial temp was lower than 39.2 C, or 10 mg/kg otherwise. D: the mean effect size for analyses comparing 10mg/kg of ibuprofen with 10 mg/kg or more for acetaminophen E: studies that examine safety that was not included in the pain or fever analyses. F: the number of patients included in the minor harm analysis. For the major harm analysis, there were 899 participants in the acetaminophen arm and 914 in the ibuprofen arm. Safety The main outcome measure for safety was the risk ratio for minor and major harms for ibuprofen vs. acetaminophen. The authors defined minor harm as the occurrence of an adverse event not leading to withdrawal from the study (e.g. nausea, sweating, or cutaneous rash). The risk ratio (RR) for minor harm was computed by dividing the number of minor harm events per patient for the ibuprofen arm by the corresponding figure for the acetaminophen treatment arm. They defined major harms as the withdrawal of a patient from the study owing to an adverse event (e.g. abdominal pain, vomiting, or hypothermia). The risk ratio for major harm was computed by dividing the number of major harm events per patient for the ibuprofen arm by the corresponding figure for the acetaminophen treatment arm. They also computed risk ratios from minor and major harm of each drug compared with placebo. The median duration of adverse effects assessment was 48 hours after commencing treatment, but there was considerable variability across studies, ranging from 4 hours to14 days. There was also considerable variability in the method of assessment of adverse effects: 1 study relied on spontaneous participant reports, 3 studies each used participant diaries or direct questioning by the investigator; and the assessment method was not reported in 10 studies. Form the minor and major harm analyses, a risk rat >1 means ibuprofen is less safe than acetaminophen. The point-estimate for the RR was 0.96 (0.68-1.36) for minor harm and 1.00 (0.55-1.82) for major harm. Q-test of heterogeneity >0.71 for each comparison. 9 studies reported minor and major harm data for placebo arm. For minor harm, the RR for acetaminophen vs. placebo was 0.79 (90%CI: 0.42-1.48); the RR for ibuprofen vs. placebo was 0.90 (90%CI: 0.68-2.03). For major harm, the RR for acetaminophen vs. placebo was 0.79 (90%CI: 0.25-3.29); the RR for ibuprofen vs. placebo was 1.51 (90%CI: 0.45-5.05).

Study	Safety assessment interval, hr	Max no of doses	Minor harm	Major harm	2 hr	4 hr	6 hr
McGaw	4	1	1.05 (0.07-16.2)	1.05 (0.02-53.6)	1.25 (0.75-2.07)	1.14 (0.80-1.62)	NA
Moore	4	1	0.80 (0.2-37.43)	0.80 (0.02-37.3)	1.31(0.70-2.47)	1.14 (0.83-1.55)	NA
Schachtel	6	1	2.93 (0.12-69.6)	2.85 (0.12-68.0)	0.91 (0.51-1.62)	1.11 (0.89-1.38)	NA
Overall	NA	NA	NA	NA	1.14 (0.82-1.58)	1.11 (0.89-1.38)	NA
Kauffman	24	1	1.00 (0.02-45.1)	1.00 (0.02-45.1)	0.37 (-0.71-1.46)	1.06(-0.11-2.23)	1.20 (0.00-2.39)
Wilson	12	1	1.00 (0.02-49.3)	1.0 (0.02-49.3)	0.00 (-0.40-0.40)	0.99 (0.57-1.42)	1.21 (0.78-1.65)
Wong	342	1	4.13 (0.47-36.6)	0.97 (0.14-6.81)	0.01 (-0.91-0.22)	-0.03 (-0.24-0.17)	0.04 (-0.17-0.24)
Walson	8	1	1.03 (0.37-2.86)	7.97 (0.43-148)	0.97 (0.40-1.53)	0.86 (0.30-1.42)	0.57 (0.03-1.120
Autret	72	12	1.78 (0.62-5.07)	1.50 (0.26-8.73)	NA	0.29 (-0.03-0.62)	NA
McIntyre	72	3	0.60(0.30-1.20)	0.85 (0.33-2.23)	NA	0.08 (-0.26-0.42)	NA
Starha	24	1	0.73 (0.02-35.6)	0.73 (0.02-35.6)	1.09 (0.54-1.64)	1.74 (1.13-2.35)	1.42 (0.84-1.99)
Van Esch	72	12	0.79 (0.31-2.05)	1.06 (0.02-51.8)	0.46 (-0.03-0.94)	0.49 (0.00-0.97)	0.31 (-0.17-0.79)
Vauzelle-Kevroedan	6	1	0.91 (0.01-3.81)	0.93 (0.02-5.46)	NA	NA	0.00 (-0.38-0.38)
Walson	24	4	NA	0.36 (0.02-	NA	NA	0.16 (-0.58-

					5.46)			0.90)
Overall	NA	NA	NA		NA	0.19 (0.05-0.33)	0.31 (0.19-0.44)	0.33 (0.19-0.47)
10 mg/kg ibuprofen only	NA	NA	NA		NA	0.34 (0.12-0.26)	0.81 (0.56-1.03)	0.66 (0.44-0.87)
Safety only	48	6	1.69 (0.42-6.82)		1.01 (0.02-50.4)	NA	NA	NA
Bertin	48	6	1.71 (0.43-6.91)		1.03 (0.02-51.1)	NA	NA	NA
Bertin	5	1	0.89 (0.36-2.19)		1.00 (0.02-49.8)	NA	NA	NA
Hamakainen	24	3	0.42 (0.04-4.31)		0.27 (0.01-6.27)	NA	NA	NA
Overall	NA	NA	0.96(0.68-1.36)		1.00 (0.55-1.82)	NA	NA	NA

There was no evidence that the drugs differ from each other or placebo in safety. Rather, these data were inconclusive on this point.

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