National Collaborating Centre for Women's and Children's Health

Urinary Tract Infection in Children
Full guideline
Document Progress Log

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Date	**Version number**	**Who amended this table**	**Action** **NOTES:** **Brief summary of changes and who made/requested.** **Change version nos. i.e. 1.1 to1.2 when comments come from different individuals; change 1.1 to 2 .1 when guideline enters different phase of development.**
10/07/06	1.1	AF	Sent to GDG. Asymptomatic bacteriuria section 6.4 added
13/07/06	1.2	AF	Minor edits
24/07/06	1.3	AF	Glossary and abbreviation updates following Imaging topic group feedback from 10/07/06
27/07/06	1.4	AF	Electronic edits included from: SAB – Prophylaxis SAB + KT – Surgery DG + topic group – Imaging
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01/08/06	2.1	AF	Changes made during meeting accepted
07/08/06	2.2	AF	JS – Recurrence edits JB – Chapter edits (predisposing factors, laboratory investigations, and antibiotics)
18/08/06	2.3	AF	SAB edits to full guideline (version 2.1)
22/08/06	2.4	AF	Re-run studies included
30/08/06	2.5	AF	LJ – Follow up edits included SAB surgery edits DG + topic group – Imaging edits (version 2.1) KT – introduction and glossary edits
31/08/06	2.6	RM	Updating health economics
05/09/06	2.7	MC	RefIDs changed following database integration
05/09/06	2.8	AF	Changes made at meeting
06/09/06	2.9	AF	DG glossary changes and structural abnormalities translation included (received 06/09)
07/09/06	3.1	AF	Uploaded on website
08/09/06	3.2	JR	HE comments added (highlighted in grey) to 7.3 - 7.6 and 6.2

18/09/06	3.3	AF	Changes made live at GDG meetings 17 and 18
19/09/06	3.4	AF	Additional changes requested at GDG meeting 17 and 18
19/09/06	3.5	AF	KVJ amended introduction included
19/09/06	4.1	AF	Changes accepted. Wendy's comments added in appropriate sections
25/09/06	4.2	AF	LJ comments to introduction added JL epidemiology chapter edits included
26/09/06	4.3	AF	Changes made at meeting 19
28/09/06	4.4	AF	KVJ intro references included MD Introduction comment included (last paragraph of 'Literature search strategy' CW changes (urine testing and prophylaxis) merged Algorithm changes made at meeting updated in text
02/10/06	4.5	AF	KVJ edits SAB edits JL glossary edits DG edits KVJ + Technical team epidemiology edits
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Urinary tract infection: diagnosis, treatment and long-term management of urinary tract infection in children

National Collaborating Centre for Women's and Children's Health

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Contents

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Stakeholder organisations

- Action for Sick Children
- Addenbrookes NHS Trust
- Airedale General Hospital - Acute Trust
- Anglesey Local Health Board
- Association for Continence Advice
- Association of Breastfeeding Mothers
- Association of Paediatric Emergency Medicine
- Association of the British Pharmaceuticals Industry,(ABPI)
- Bard Limited
- Barnet Primary Care Trust
- Barnsley Primary Care Trust
- Barts and the London NHS Trust - London
- Bayer Healthcare PLC
- Bedfordshire & Hertfordshire NHS Strategic Health Authority
- Birmingham Children's Hospital
- British Association for Accident and Emergency Medicine
- British Association for Paediatric Nephrology
- British Association of Paediatric Surgeons
- British National Formulary (BNF)
- British Nuclear Medicine Society
- British Psychological Society, The

- British Society for Antimicrobial Chemotherapy
- British Society of Paediatric Radiology
- Calderdale and Huddersfield NHS Trust
- Calderdale Royal Hospital
- CASPE
- CEMACH
- Central Liverpool Primary Care Trust
- Centre for Reviews and Dissemination
- CIS'ters
- Coloplast Limited
- Commission for Social Care Inspection
- Connecting for Health
- Conwy & Denbighshire NHS Trust
- Co-operative Pharmacy Association
- Craven Harrogate and Rural District Primary Care Trust
- Croydon Primary Care Trust
- Department of Health
- East Cambridgeshire and Fenland Primary Care Trust
- Eastbourne Downs Primary Care Trust
- Faculty of Public Health
- Gloucestershire Hospital NHS Trust
- Good Hope Hospitals NHS Trust
- Great Ormond Street Hospital for Children NHS Trust

- Health Protection Agency
- Health Protection Scotland
- Healthcare Commission
- Heart of England NHS Foundation Trust
- Hertfordshire Partnership NHS Trust
- Hospital Infection Society
- Infection Control Nurses Association of the British Isles
- Institute of biomedical Science
- Leeds Teaching Hospitals NHS Trust
- Luton and Dunstable Hospital NHS Trust
- Maidstone and Tunbridge Wells NHS Trust
- Medicines and Healthcare Products Regulatory Agency (MHRA)
- Mid Essex Hospitals NHS Trust
- National Kidney Federation (NFK)
- National Kidney Research Fund, The
- National Patient Safety Agency
- National Public Health Service - Wales
- Neonatal & Paediatric Pharmacists Group (NPPG)
- Newcastle Primary Care Trust
- Newcastle Upon Tyne Hospitals NHS Trust
- NHS Direct
- NHS Quality Improvement Scotland
- North Tyneside Primary Care Trust

- Northwest London Hospitals NHS Trust
- Nottingham City Hospital
- Patient and Public Involvement Programme for NICE
- PERIGON (formerly The NHS Modernisation Agency)
- Powys Local Health Board
- Princess Alexandra Hospital NHS Trust
- Prodigy
- PromoCon (Disabled Living)
- Q-Med (UK) Ltd
- Queen Elizabeth Hospital NHS Trust (Woolwich)
- Regional Public Health Group - London
- Rotherham Primary Care Trust
- Royal Bolton Hospitals NHS Trust
- Royal College of General Practitioners
- Royal College of General Practitioners Wales
- Royal College of Nursing
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists
- Royal College of Radiologists
- Royal College of Surgeons of England
- Royal Liverpool Children's NHS Trust
- Royal United Hospital, Bath NHS Trust
- Sandwell & West Birmingham Hospitals NHS Trust

- Scottish Intercollegiate Guidelines Network (SIGN)
- Sheffield Children's Hospital NHS Trust
- Sheffield South West Primary Care Trust
- Society and College of Radiographers
- South & Central Huddersfield Primary Care Trust
- South Birmingham Primary Care Trust
- South East Sheffield Primary Care Trust
- South Warwickshire General Hospitals NHS Trust
- Southport & Ormskirk Hospital NHS Trust
- Specialist Advisory Committee on Antimicrobial Resistance (SACAR)
- St Mary's Hospital, Isle of Wight Healthcare NHS Trust
- Staffordshire Moorlans Primary Care Trust
- Stockport Primary Care Trust
- Tameside and Glossop Acute Services NHS Trust
- The David Lewis Centre
- The Medway NHS Trust
- The North West London Hospitals NHS Trust
- The Royal Society of Medicine
- The Royal West Sussex Trust
- The Survivors Trust
- UK Specialised Services Public Health Network
- University College London Hospitals NHS Trust
- University Hospital Birmingham NHS Trust

- Welsh Assembly Government
- West of Cornwall Primary Care Trust
- Whipps Cross University Hospital NHS Trust
- Wyre Forest Primary Care Trust

Abbreviations

ARR	Absolute risk reduction
CAT	Computed axial tomography
CCT	Control clinical trial
CER	Control event rate
cfu	Colony forming unit
CI	Confidence interval
CKD	Chronic kidney disease
CRP	C-reactive protein
CP	Chronic pyelonephritis
CUS	Cystourethrosonography
CT	Computed Tomography
DAH	Douleur Aique du Nouveaune (Neonatal pain score)
DGH	District General Hospital
DOR	Diagnostic odds ratio
DMSA	Dimercapto succinic acid.
DRC	Direct radionuclide cystography
EDTA	99-Tc-chromium-ethylene-diamine-tetraacetic acid
EER	Experimental Event Rate
eGFR	Estimated glomerular filtration rate
EL	Evidence Level
ESR	Erythrocyte sedimentation rate

ESRD	End stage renal disease
GDG	Guideline Development Group
GFR	Glomerular filtration rate
GP	General Practitioner
GPP	Good practice point
hpf	High power field
HTA	Health Technology Appraisal
IL-1ß	Interleukin-1 beta
IL-6	Interleukin-6
IM	Intramuscular
IRC	Indirect radionuclide cystogram
IQR	Inter-quartile range
IV	Intravenous
IVP	Intravenous pyelogram
IVU	Intravenous urogram
LE	Leukocyte esterase
LR+	Positive likelihood ratio
LR-	Negative likelihood ratio
MAG3	Mercapto-acetyltriglycine
MCUG	Micturating cystourethrogram
MRI	Magnetic resonance imaging
NAG	N-acetyl-beta-glucosaminidase
NCC-WCH	National Collaborating Centre for Women's and Children's

	Health
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NNH	Number needed to harm
NNT	Number needed to treat
NSF	National Service Framework
NPV	Negative predictive value
OR	Odds ratio
PDU	Power doppler ultrasound
PHLS	Public Health Laboratory Service
PMP	Per million population
PPIP	Patient and Public Involvement Programme
PPV	Positive predictive value
QALY	Quality Adjusted Life Years
RCT	Randomised controlled trial
ROC	Receiver operator characteristic
RN	Reflux nephropathy
RR	Relative risk (or risk ratio)
SD	Standard deviation
SEC	Squamous epithelial cell
SPA	Suprapubic aspiration
SROC	Summary receiver operator characteristic
STING	Submucosal Teflon injection

TNF-a	Tumour Necrosis Factor - alpha
UTI	Urinary tract infection
VCUG	Voiding cystourethrogram
VUR	Vesicoureteric reflux
VUS	Voiding urosonography
WBC	White blood cell
WMD	Weighted mean difference

1 Glossary of terms

Absolute risk Measures the probability of an event or outcome occurring (e.g. an adverse reaction to the drug being tested) in aa group of people or a population under study. Studies that compare two or more groups of patients may report results in terms of the *Absolute Risk Reduction (ARR)*. 1/ARR is a calculation that gives us Numbers Needed to Treat (see later). Absolute risk reductions are similar to Relative risk reductions for common events but differ for rare events e.g If a group of children has a risk of recurrent UTI of 15% when untreated, but this reduces to 10% as a result of intervention, then the Absolute risk reduction (ARR) is 5% (15-10%) but the Relative risk reduction (RRR) is 33% (5/15 x100%). If, however, the reduction is from 100% to 95 % both the ARR and the RRR are 5%. In both cases the NNT is unchanged at 20 (1/5%).

Absolute Risk Reduction The ARR is the difference in the risk of an event occurring between two groups of patients in a study – for example if 6% of patients die after receiving a new experimental drug and 10% of patients die after having the old drug treatment then the ARR is 10% - 6% = 4%. Thus by using

	the new drug instead of the old drug 4% of patients can be prevented from dying. Here the ARR measures the risk reduction associated with a new treatment. See also *Absolute risk*.
Acute Pyelonephritis	A bacterial infection of the upper urinary tract.
Acute sector	Hospital-based health services which are provided on an in-patient, day case or out-patient basis.
Acute trust	A trust is an NHS organisation responsible for providing a group of healthcare services. An acute trust provides hospital services (but not mental health hospital services which are provided by a *mental health trust*).
Allied health professionals	Healthcare professionals, other than doctors and nurses, directly involved in the provision of healthcare. Includes several groups such as physiotherapists, occupational therapists, dieticians, etc. (Formerly known as professions allied to medicine or PAMs.)
Antibiotic prophylaxis	See *Prophylaxis, antibiotic*
Applicability	The extent to which the results of a study or review can be applied to the target population for a clinical guideline.
Appraisal of evidence	Formal assessment of the quality of research evidence and its relevance to the clinical question or guideline

	under consideration, according to predetermined criteria.
Asymptomatic bacteriuria	The presence of bacteria in the urine without the presentation of symptoms specific to the disease.
Bacteriuria	The presence of bacteria in the urine with or without consequent urinary tract infection
Best available evidence	The strongest research evidence available to support a particular guideline recommendation.
Bias	Influences on a study that can lead to invalid conclusions about a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it actually doesn't. Bias can occur by chance or as a result of *systematic* influences caused by the design and/or execution of a study. Bias can occur at different stages in the research process, e.g. in the collection, analysis, interpretation, publication or review of research data. For examples see *Selection bias, Performance bias, Information bias, , Publication bias*.
Bladder instability	Inappropriate bladder contractions, resulting in an involuntary loss of urine.
Blinding or masking	The practice of keeping the investigators or subjects of a study ignorant of the group to which a subject has been assigned. For example, a clinical trial in which the

	participating patients or their doctors are unaware of whether they (the patients) are taking the experimental drug or a placebo (dummy treatment). The purpose of 'blinding' or 'masking' is to protect against *bias*. See also *Double blind study, Single blind study, Triple blind study*.
C-reactive protein (CRP)	A protein produced by the liver that is normally present in trace amounts in the blood but is elevated during episodes of inflammation and after tissue damage.
Case-control study	A study that starts with the identification of a group of individuals sharing the same characteristics (e.g. people with a particular disease) and a suitable comparison (control) group (e.g. people without the disease). All subjects are then assessed with respect to things that happened to them in the past, e.g. things that might be related to getting the disease under investigation. Such studies are also called *retrospective* as they look back in time from the outcome to the possible causes.
Case report (or case study)	Detailed report on one patient (or case), usually covering the course of that person's disease and their response to treatment.
Case series	Description of several cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (*control*) group of

	patients.
CAT scan	See *CT scan*
Catheter	A tubular medical device for insertion into a duct, blood vessel, hollow organ, or body cavity for injecting or withdrawing fluids for diagnostic or therapeutic purposes
Causal relationship	Describes the relationship between *two variables* whenever it can be established that one causes the other. For example there is a causal relationship between a treatment and a disease if it can be shown that the treatment changes the course or outcome of the disease. Usually *randomised controlled trials* are needed to ascertain causality. Proving cause and effect is much more difficult than just showing an association between two variables. For example, if it happened that everyone who had eaten a particular food became sick, and everyone who avoided that food remained well, then the food would clearly be associated with the sickness. However, even if leftovers were found to be contaminated, it could not be proved that the food caused the sickness – unless all other possible causes (e.g. environmental factors) had been ruled out.
Checklist	See *Study checklist*.
Chronic Kidney	Previously known as chronic renal failure (CRF), or

Disease (CKD)	Chronic renal insufficiency, The stages of chronic kidney disease are as follows: Stage 1: Kidney damage but normal kidney function (GFR > 90 ml/min/m2) Stage 2: Mild decrease of GFR (60-89) Stage 3: Moderate decrease of GFR (30-59) Stage 4: Severe decrease in GFR (15-29) Stage 5: Kidney failure (GFR <15 or dialysis)[1]
Chronic pyelonephritis	Fibrotic scarred area of renal parenchyma.
Clinical audit	A *systematic* process for and monitoring standards of clinical care. Whereas 'guidelines' define what the best clinical practice should be, 'audit' investigates whether best practice is being carried out. Clinical audit can be described as a one-off event, a cycle or a spiral. Within aa cycle there are stages that follow a systematic process of establishing best practice, measuring care against specific criteria, taking action to improve care, and monitoring to sustain improvement. The spiral suggests that as the process continues, each cycle aspires to a higher level of quality.
Clinical effectiveness	The extent to which a specific treatment or intervention, when used under usual or everyday conditions, has a

	beneficial effect on the course or outcome of disease compared to no treatment or other routine care. (Clinical trials that assess effectiveness are sometimes called management trials.) Clinical 'effectiveness' is not the same as *efficacy*.
Clinical governance	A framework through which NHS organisations are accountable for both continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish.
Clinical impact	The effect that a guideline recommendation is likely to have on the treatment, or treatment outcomes, of the target population.
Clinical importance	The importance of a particular guideline recommendation to the clinical management of the target population.
Clinical question	This term is sometimes used in guideline development work to refer to the questions about treatment and care that are formulated in order to guide the search for research evidence. When a clinical question is formulated in a precise way, it is called a *focused question*.
Clinical trial	A research study conducted with patients which tests out a drug or other intervention to assess its effectiveness and safety. Each trial is designed to answer scientific

	questions and to find better ways to treat individuals with a specific disease. This general term encompasses *controlled clinical trials* and *randomised controlled trials*.
Clinician	A health care professional providing patient care, e.g. doctor, nurse, physiotherapist.
Cluster	A group of patients, rather than an individual, used as the basic unit for investigation. See also *Cluster design, Cluster randomisation*.
Cluster design	Cluster designs are those where research subjects are not sampled or selected independently, but in a group. For example a clinical trial where patients in a general practice are allocated to the same intervention; the general practice forming a cluster. See also *Cluster, Cluster randomisation*.
Cluster randomisation	A study in which groups of individuals (e.g. patients in a GP surgery or on a hospital ward) are randomly allocated to treatment groups. Take, for example, a smoking cessation study of two different interventions – leaflets and teaching sessions. Each GP surgery within the study would be randomly allocated to administer one of the two interventions. See also *Cluster, Cluster design*.
Cochrane Collaboration	An international organisation in which people find, appraise and review specific types of studies called

randomised controlled trials. The Cochrane Database of Systematic Reviews contains regularly updated reviews on a variety of health issues and is available electronically as part of the *Cochrane Library*.

Cochrane Library The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of *randomised controlled trials* prepared by the *Cochrane Collaboration*). The Cochrane Library is available on CD-ROM and the Internet.

Cohort A group of people sharing some common characteristic (e.g. patients with the same disease), followed up in a research study for a specified period of time.

Cohort study An observational study that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or interventions that patients received. Thus within the study group, subgroups of patients are identified (from information collected about patients) and these groups are compared with respect to outcome, e.g. comparing mortality between one group that received a specific treatment and one group which did not (or between two

groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent' or 'prospective' cohort study) or identified from past records and followed forward from that time up to the present (a 'historical' or 'retrospective' cohort study). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.

Colony forming unit (cfu) Colony-forming unit (cfu) is a measure of viable bacterial numbers. Unlike in direct microscopic counts where all cells, dead and living, are counted, the cfu measures viable cells. A sample is spread or poured on a surface of an agar plate, left to incubate and the number of colonies formed are counted. The number of cfu's is not an exact measure of numbers of viable cells, as a cfu may contain more cells.

Combined modality Use of different treatments in combination (for example surgery, chemotherapy and radiotherapy used together for cancer patients).

Commercial 'in Information (e.g. the findings of a research project)

confidence' material	defined as 'confidential' as its public disclosure could have an impact on the commercial interests of a particular company. (Academic 'in confidence' material is information [usually work produced by a research or professional organisation] that is pending publication.)
Co-morbidity	Co-existence of a disease or diseases in the people being studied in addition to the health problem that is the subject of the study.
Computed axial tomography scan	A method of body imaging using x-rays and computer algorithms to generate cross-sectional and three-dimensional models of organs. Also known as Computed axial tomography (CAT) scan or CT scan
Concomitant	Occurring during the same time period, usually referring to secondary symptoms that occur with a main symptom.
Confidence interval	A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that are consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with

	too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95%' confidence interval as the range of effects within which we are 95% confident that the true effect lies.
Confounder or confounding factor	Confounders are variables that are both associated with the condition being studied, and have an independent effect on its outcomes. It can contribute to misleading findings if it is not understood or appropriately dealt with. For example, if a group of people exercising regularly and a group of people who do not exercise have an important age difference then any difference found in outcomes about heart disease could well be due to one group being older than the other rather than due to the exercising. Age is the confounding factor here and the effect of exercising on heart disease cannot be assessed without adjusting for age differences in some way.
Consensus development conference	A technique used for the purpose of reaching an agreement on a particular issue. It involves bringing together a group of about 10 people who are presented with evidence by various interest groups or experts who are not part of the decision making group. The group then retires to consider the questions in the light of the

	evidence presented and attempts to reach a consensus. See also *Consensus methods*.
Consensus methods	A variety of techniques that aim to reach an agreement on a particular issue. Formal consensus methods include *Delphi* and *nominal group* techniques, and *consensus development conferences*. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic.
Consensus statement	A statement of the advised course of action in relation to a particular clinical topic, based on the collective views of a body of experts.
Considered judgement	The application of the collective knowledge of a guideline development group to a body of evidence, to assess its applicability to the target population and the strength of any recommendation that it would support.
Consistency	The extent to which the conclusions of a collection of studies used to support a guideline recommendation are in agreement with each other. See also *Homogeneity*.
Control Event Rate	See *Event rate*.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a

	new drug.
Controlled clinical trial (CCT)	A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a *randomised controlled trial*.
Cost benefit analysis	A type of *economic evaluation* where both costs and benefits of health care treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost effectiveness	Value for money. A specific health care treatment is said to be 'cost-effective' if it gives a greater health gain than could be achieved by using the resources in other ways.
Cost effectiveness analysis	A type of *economic evaluation* comparing the costs and the effects on health of different treatments. Health effects are measured in 'health-related units', for example, the cost of preventing one additional heart attack.
Cost utility	A special form of *cost effectiveness analysis* where health

analysis	effects are measured in *quality adjusted life years*. A treatment is assessed in terms of its ability to both extend life and to improve the quality of life.
Crossover study design	A study comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another. For example, for a comparison of treatments A and B, half the participants are randomly allocated to receive them in the order A, B and half to receive them in the order B, A. A problem with this study design is that the effects of the first treatment may carry over into the period when the second is given. Therefore a crossover study should include an adequate 'wash-out' period, which means allowing sufficient time between stopping one treatment and starting another so that the first treatment has time to wash out of the patient's system.
Cross-sectional study	The observation of a defined set of people at a single point in time or time period – a snapshot. (This type of study contrasts with a *longitudinal study* which follows a set of people over a period of time.)
CT scan	See *Computed axial tomography scan*
Culture	A technique of maintaining or growing bacteriological materials in controlled laboratory conditions.

Cystitis	Inflammation of the bladder
Cystography	See *Micturating cystourethrogram (MCUG)*
Cystourethrogram	See *Micturating cystourethrogram (MCUG)*
Cystosonography/ cystourethrosonography	Method of looking for VUR using ultrasound and sonographic contrast medium instilled into the bladder. The urinary bladder is catheterised and a mixture of water and sonographic contrast medium (microparticles in suspension) are instilled. The renal tract is scanned as the fluid is instilled and reflux is identified by seeing echoes from these particles in the ureters and renal collecting systems. It has the advantage that no ionising radiation is used and that the anatomy of the renal tract can be assessed at the same time.
Data set	A list of required information relating to a specific disease.
Decision analysis	Decision analysis is the study of how people make decisions or how they *should* make decisions. There are several methods that decision analysts use to help people to make better decisions, including *decision trees*.
Decision tree	A decision tree is a method for helping people to make better decisions in situations of uncertainty. It illustrates the decision as a succession of possible actions and

	outcomes. It consists of the probabilities, costs and health consequences associated with each option. The overall effectiveness or overall cost-effectiveness of different actions can then be compared.
Declaration of interest	A process by which members of a working group or committee 'declare' any personal or professional involvement with a company (or related to a technology) that might affect their objectivity e.g. if their position or department is funded by a pharmaceutical company.
Delphi method	A technique used for the purpose of reaching an agreement on a particular issue, without the participants meeting or interacting directly. It involves sending participants a series of postal questionnaires asking them to record their views. After the first questionnaire, participants are asked to give further views in the light of the group feedback. The judgements of the participants are aggregated, sometimes after weighting for expertise. See also *Consensus methods*.
Diagnostic odds ratio (DOR)	Expresses the odds of positive test results in patients with disease compared to patients without the disease. The diagnostic odds ratio is defined as the positive likelihood ratio divided by negative likelihood ratio.
Diagnostic study	A study to assess the effectiveness of a test or

	measurement in terms of its ability to accurately detect or exclude a specific disease.
Dipstick	A diagnostic tool, consisting of a chemically sensitive strip of paper used to identify one of more constituents, such as white blood cells, nitrites, glucose or protein, of urine by immersion.
Direct radionuclide cystogram (DRC)	Direct radionuclide cystogram (DRC) - a small dose of a radionuclide (pertechnetate – Tc^{99m}) diluted in water is instilled into the urinary bladder through a catheter placed for this purpose. Images of the bladder and kidneys are taken as the bladder is filled and during voiding. This test is sensitive for small degrees of reflux but lacks anatomic detail of an MCUG. The radiation dose is small (0.05mSv) – approximately 2-3 days worth of exposure to natural background radiation.
Dimercapto succinic acid scintigraphy (DMSA)	DMSA is a radionuclide scan of the kidneys utilising dimercaptosuccinic acid. It is used to identify renal parenchymal defects. Intravenously injected Tc99m labelled DMSA binds to the kidneys and emits gamma rays which are detected by a camera. The outline and distribution of renal tissue in can be seen and scars are visible as ‘defects’ on these images. Uptake of DMSA by each kidney can be

	compared to estimate the relative function of each. The radiation dose incurred is approximately (1mSv) equivalent to 4 months of natural background radiation (about 40-50 chest radiographs).
Dominance	A term used in health economics describing when an option for treatment is both less clinically effective and more costly than an alternative option. The less effective and more costly option is said to be 'dominated'.
Doppler ultrasound	See *Ultrasound*
Double blind study	A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment or intervention the subject is receiving. The purpose of blinding is to protect against bias.
Dysuria	The difficult or painful discharge of urine.
Dysfunctional elimination syndrome	Dysfunctional elimination syndrome refers to an abnormal pattern of elimination of unknown etiology characterized by bowel and bladder incontinence and withholding.
Economic evaluation	A comparison of alternative courses of action in terms of both their costs and consequences. In *health economic* evaluations the consequences should include health outcomes.
Effectiveness	See *Clinical effectiveness*.

Efficacy	The extent to which a specific treatment or intervention, under ideally controlled conditions (e.g. in a laboratory), has a beneficial effect on the course or outcome of disease compared to no treatment or other routine care.
Elective	Name for clinical procedures that are regarded as advantageous to the patient but not urgent.
Empirical	Based directly on experience (observation or experiment) rather than on reasoning alone.
Encopresis	The voluntary or involuntary passage of stools in inappropriate places.
End stage kidney disease	See *End stage renal disease*
End stage renal disease (ESRD)	The final stage of kidney failure that is marked by the complete, or nearly complete, irreversible loss of kidney function.
End stage renal failure	See *End stage renal disease*
Epidemiology	Study of diseases within a population, covering the causes and means of prevention.
Erythrocyte sedimentation rate (ESR)	A non-specific screening test for various diseases that measures the distance (in millimetres) that red blood cells settle in unclotted blood toward the bottom of a specially marked test tube.

Event rate	The proportion of patients in a group for whom a specified health event or outcome is observed. Thus, if out of 100 patients, the event is observed in 27, the event rate is 0.27 or 27%. Control Event Rate (CER) and Experimental Event Rate (EER) are the terms used in *control* and experimental groups of patients respectively.
Evidence based	The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.
Evidence based clinical practice	Evidence based clinical practice involves making decisions about the care of individual patients based on the best research evidence available rather than basing decisions on personal opinions or common practice (which may not always be evidence based). Evidence based clinical practice therefore involves integrating individual clinical expertise and patient preferences with the best available evidence from research
Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Exclusion criteria	See *Selection criteria*.
Experimental Event Rate (EER)	See *Event rate*.

Experimental study	A research study designed to test if a treatment or intervention has an effect on the course or outcome of a condition or disease - where the conditions of testing are to some extent under the control of the investigator. *Controlled clinical trial* and *randomised controlled trial* are examples of experimental studies.
Experimental treatment	A treatment or intervention (e.g. a new drug) being studied to see if it has an effect on the course or outcome of a condition or disease.
External validity	The degree to which the results of a study hold true in non-study situations, e.g. in routine clinical practice. May also be referred to as the *generalisability* of study results to non-study patients or populations.
Extrapolation	The application of research evidence based on studies of a specific population to another population with similar characteristics.
Febrile	See *Fever*
Fever	The elevation of body temperature above normal daily variation.
Focus group	A *qualitative research* technique (originally a market research technique). It is a method of group interview or discussion, commonly involving 6–12 people focused around a particular issue or topic. The method explicitly

includes and uses the group interaction to generate data.

Focused question A study question that clearly identifies all aspects of the topic that are to be considered while seeking an answer. Questions are normally expected to identify the patients or population involved, the treatment or intervention to be investigated, what outcomes are to be considered, and any comparisons that are to be made. E.g. Do antibiotics (intervention) eliminate bacteriuria (outcome) in children with urinary tract infection (population) compared with alternative therapies (comparison)? See also *Clinical question*.

Forest plot A graphical display of results from individual studies on a common scale, allowing visual comparison of results and examination of the degree of *heterogeneity* between studies.

Funnel plot Funnel plots are simple scatter plots on a graph. They show the treatment effects estimated from separate studies on the horizontal axis against a measure of sample size on the vertical axis. *Publication bias* may lead to asymmetry in funnel plots.

Generalisability The extent to which the results of a study hold true for a population of patients beyond those who participated in the research. See also *External validity*.

Glomerular filtration rate (GFR)	Measure of the kidneys' ability to filter and remove waste products.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available.
Good practice point (GPP)	Recommended good practice based on the expert experience of the guideline development group (and possibly incorporating the expertise of a wider reference group). A guideline development group may produce a 'Good practice point' (rather than an evidence based recommendation) on an important topic when there is a lack of research evidence.
Grade of recommendation	A code (e.g. A, B, C) linked to a guideline recommendation, indicating the strength of the evidence supporting that recommendation.
Grey literature	Reports that are unpublished or have limited distribution, and are not included in bibliographic retrieval systems.
Guideline	A systematically developed tool which describes aspects of a patient's condition and the care to be given. A good guideline makes recommendations about treatment and care, based on the best research available, rather than opinion. It is used to assist clinician and patient decision-making about appropriate health care for specific clinical conditions.

Guideline recommendation	Course of action advised by the guideline development group on the basis of their assessment of the supporting evidence.
Haematuria	The presence of blood in the urine.
Haemocytometer	A ruled microscope slide used to count red and white blood cells in body fluids
Health economics	A branch of economics which studies decisions about the use and distribution of health care resources.
Health technology	Health technologies include medicines, medical devices such as artificial hip joints, diagnostic techniques, surgical procedures, health promotion activities (e.g. the role of diet versus medicines in disease management) and other therapeutic interventions.
Health Technology Appraisal (HTA)	A health technology appraisal, as undertaken by NICE, is the process of determining the clinical and cost effectiveness of a *health technology*. NICE health technology appraisals are designed to provide patients, health professionals and managers with an authoritative source of advice on new and existing health technologies.
Heterogeneity	Or lack of *homogeneity*. The term is used in *meta-analyses* and *systematic reviews* when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of

	treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of *variables* or duration of follow-up.
HG tube	Commercially available urine collection tube.
Hierarchy of evidence	An established hierarchy of study types, based on the degree of certainty that can be attributed to the conclusions that can be drawn from a well conducted study. Well-conducted *randomised controlled trials* (RCTs) are at the top of this hierarchy. (Several large statistically significant RCTs which are in agreement represent stronger evidence than say one small RCT.) Well-conducted studies of patients' views and experiences would appear at a lower level in the hierarchy of evidence.
Homogeneity	This means that the results of studies included in a *systematic review* or *meta analysis* are similar and there is no evidence of *heterogeneity*. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance. See also *Consistency*.
Hydronephrosis	Distension or dilation of the pelvis and calyces of the

	kidney.
Hypertension, renal	See *Renal hypertension*
Iatrogenic	Any adverse condition in a patient occurring as the result of treatment by a health professional.
Incidence	The number of new cases of a given disease during a given period in a specified population. It also is used for the rate at which new events occur in a defined population.
Inclusion criteria	See *Selection criteria*.
In depth interview	A *qualitative research* technique. It is a face to face conversation between a researcher and a respondent with the purpose of exploring issues or topics in detail. Does not use pre-set questions, but is shaped by a defined set of topics or issues.
Indirect radionuclide cystogram (IRC)	Indirect radionuclide cystogram (IRC) – can be performed as a supplement to a standard MAG 3 scan in toilet trained children. At the end of the MAG 3 scan the bladder contains the secreted radionuclide mixed with urine. Images are obtained as the child voids urine, and an objective assessment of bladder emptying can be made. Any reflux of MAG 3 from the bladder to the kidneys can also be

	identified. Though not as sensitive for the detection of reflux as direct forms of cystography (DRC, MCUG, cystosonography), the need for bladder catheterisation is avoided.
Information bias	Pertinent to all types of study and can be caused by inadequate questionnaires (e.g. difficult or biased questions), observer or interviewer errors (e.g. lack of *blinding*), response errors (e.g. lack of *blinding* if patients are aware of the treatment they receive) and measurement error (e.g. a faulty machine).
Intention to treat analysis	An analysis of a clinical trial where patients are analysed according to the group to which they were initially randomly allocated, regardless of whether or not they had dropped out, fully complied with the treatment, or crossed over and received the alternative treatment. Intention-to-treat analyses are favoured in assessments of clinical effectiveness as they mirror the non-compliance and treatment changes that are likely to occur when the treatment is used in practice.
Interleukin-1 beta (IL-1B)	A soluble factor produced by monocytes, macrophages, and other cells which activates T-lymphocytes and potentiates their response to mitogens or antigens. IL-1

	consists of two distinct forms, IL-1 alpha and IL-1 beta which perform the same functions but are distinct proteins. The biological effects of IL-1 include the ability to replace macrophage requirements for T-cell activation.
Interleukin-6 (IL-6)	A cytokine that stimulates the growth and differentiation of human B-cells and is also a growth factor for hybridomas and plasmacytomas. It is produced by many different cells including T-cells, monocytes, and fibroblasts. A single chain 25 kD cytokine originally described as a pre B-cell growth factor, now known to have effects on a number of other cells including T-cells which are also stimulated to proliferate.
Internal validity	Refers to the integrity of the study design.
Inter quartile range (IQR)	In descriptive statistics, the interquartile range (IQR) is the difference between the third and first quartiles and is a measure of statistical dispersion. The interquartile range is a more stable statistic than the range, and is often preferred to that statistic. Since 25% of the data are less than or equal to the first quartile and 25% are greater than or equal to the third quartile, the difference is the length of an interval that includes about half of the data. This difference should be measured in the same units as the data
Intervention	Healthcare action intended to benefit the patient, e.g. drug treatment, surgical procedure, psychological therapy, etc.

Interventional procedure	A procedure used for diagnosis or treatment that involves making a cut or hole in the patient's body, entry into a body cavity or using electromagnetic radiation (including X-rays or lasers). The National Institute for Clinical Excellence (NICE) has the task of producing guidance about whether specific interventional procedures are safe enough and work well enough for routine use.
Intramuscular (IM)	Administration into a muscle.
Intravenous (IV)	Administration into a vein.
Intravenous Pyelogram (IVP)	See IVU
Intravenous Urogram (IVU)	Intravenous urography involves the intravenous injection of a radiographic contrast medium (iodine based) that is taken up and excreted by the kidneys. X-ray images of the abdomen are then taken showing detailed anatomy of the urinary tract. The dose of radiation is moderately high and there is a small but real risk of an allergic reaction to the contrast medium. It is no longer used for the routine evaluation of children with urinary tract infection.
Leukocyte esterase (LE)	An enzyme present in white blood cells which can be detected in the urine during infection.
Level of evidence	A code (e.g. 1++, 1+) linked to an individual study,

	indicating where it fits into the *hierarchy of evidence* and how well it has adhered to recognised research principles.
Likelihood ratio	See *positive likelihood ratio* or *negative likelihood ratio*
Literature review	A process of collecting, reading and assessing the quality of published (and unpublished) articles on a given topic.
Longitudinal study	A study of the same group of people at more than one point in time. (This type of study contrasts with a *cross sectional study* which observes a defined set of people at a single point in time.)
MAG 3 scan	See *Mercapto-acetyltriglycine (MAG 3) scan*
Magnetic resonance imaging (MRI)	Magnetic resonance imaging uses a combination of radiowaves and strong magnetic fields to generate detailed images of the body. In many ways it is an ideal technique for children as it does not utilise ionising radiation (X- and gamma-rays). It has potential to define clearly the anatomy of the kidneys, ureters and bladder, and can provide some functional information. Its role in the management of urinary tract infection in children is yet to be established.
Masking	See *Blinding*.
Mental health trust	A trust is an NHS organisation responsible for providing a group of healthcare services. A mental health trust provides both hospital and community based mental

	health services.
Mercapto-acetyltriglycine (MAG 3) scan	Also known as dynamic renography, MAG 3 is a radionuclide scan of the kidneys utilising methylacyltriglycine. It is used to evaluate drainage of urine from the kidneys into the bladder. Intravenously injected Tc^{99m} labelled MAG 3 is taken up by the kidneys, is secreted into the renal collecting system and drains into the bladder. The radiation dose incurred is approximately equivalent to 2 months of natural background radiation (about 20-25 chest radiographs). The MAG 3 scan can be extended by imaging while the child voids urine – an indirect radionuclide cystogram.
Meta analysis	Results from a collection of independent studies (investigating the same treatment) are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. Where studies are not compatible e.g. because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to statistically pool results in this way. See also *Systematic review* & *Heterogeneity*.

Methodology	The overall approach of a research project, e.g. the study will be a *randomised controlled trial*, of 200 people, over one year.
Methodological quality	The extent to which a study has conformed to recognised good practice in the design and execution of its research methods.
Microscopy	The use of a microscope for visualizing material that cannot be seen by the unaided eye.
Micturating cystourethrogram (MCUG)	The micturating cystourethrogram is the most common test used in the UK for the detection of vesico-ureteric reflux in children. It also provides good anatomic detail of the bladder and urethra. Radiographic contrast medium is instilled into the bladder through a urethral catheter and X-ray images are taken showing the bladder, urethra and any reflux present. The radiation dose from MCUG is greater than for DRC but the introduction of dose reduction techniques can minimise this. Even so the estimated dose for a 1 year old infant is 1mSv, equivalent to about 4 months of natural background radiation.
Morbidity	A diseased state or symptom
Multicentre study	A study where subjects were selected from different locations or populations, e.g. a co-operative study

	between different hospitals; an international collaboration involving patients from more than one country.
Multivariable analysis	Multivariable analysis is a tool for determining the relative contributions of different causes to a single event.
N-acetyl-beta-glucosaminidase (NAG)	An enzyme marker of renal tubular damage
Negative likelihood ratio (LR-)	The negative likelihood ratio describes the probability of having a negative test result in the diseased population compared to that of a non-diseased population and corresponds to the ratio of the false negative rate divided by the true negative rate (1-sensitivity/specificity).
Negative predictive value (NPV)	The negative predictive value expresses the probability that a patient with a negative test result does not have the target condition.
Nitrite	A nitrite is a chemical compound, being either an ionic or a covalent compound, i.e. a salt or an ester of nitrous acid.
Nominal group technique	A technique used for the purpose of reaching an agreement on a particular issue. It uses a variety of postal and direct contact techniques, with individual judgements being aggregated statistically to derive the group judgement. See also *Consensus methods*.

Non-experimental study	A study based on subjects selected on the basis of their availability, with no attempt having been made to avoid problems of bias. Excuse my ignorance, but surely a non-experimental study is merely one which does not involve active intervention, and one cannot draw inferences on selection (which is a separate issue)
Non-systematic review	See *Review*.
Nosocomial infection	Hospital acquired infection
Number Needed to Harm (NNH)	See *Number Needed to Treat*
Number Needed to Treat (NNT)	This measures the impact of a treatment or intervention. It states how many patients need to be treated with the treatment in question in order to prevent an event which would otherwise occur. E.g. if the NNT=4, then 4 patients would have to be treated to prevent a particular outcome .. The closer the NNT is to 1, the better the treatment is. Analogous to the NNT is the Number Needed to Harm (NNH),which is the number of patients that would need to receive a treatment to cause one additional adverse event. e.g. if the NNH=4, then 4 patients would have to be treated for adverse event to occur.

Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and study participants.
Observation	Observation is a research technique used to help understand complex situations. It involves watching, listening to and recording behaviours, actions, activities and interactions. The settings are usually natural, but they can be laboratory settings, as in psychological research.
Observational study	In research about diseases or treatments, this refers to a study in which nature is allowed to take its course. Changes or differences in one characteristic (e.g. whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (e.g. whether or not they died), without the intervention of the investigator. There is a greater risk of *selection bias* than in *experimental studies*. As per comments on non-experimental- this is often true but is a function of selection criteria, rather than the type of study
Odds ratio (OR)	Odds are a way of representing probability, especially familiar for betting. In recent years odds ratios have become widely used in reports of clinical studies that do use indirect calculations eg case-Control studies, or in regression techniques. They provide an estimate (usually

with a *confidence interval*) for the effect of a treatment. Odds are used to convey the idea of 'risk' and an odds ratio of 1 between two treatment groups would imply that the risks of an adverse outcome were the same in each group. For rare events the odds ratio and the *relative risk* (which uses actual risks and not odds) will be very similar. See also *Relative risk, Risk ratio*.

Off-label prescribing When a drug or device is prescribed outside its *specific indication*, to treat a condition or disease for which it is not specifically licensed.

Outcome The end result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/ treatment/ rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Peer review Review of a study, service or recommendations by those with similar interests and expertise to the people who produced the study findings or recommendations. Peer reviewers can include professional and/ or patient/ carer representatives.

Performance bias Systematic differences in care provided apart from the

intervention being evaluated. For example, if study participants know they are in the *control group* they may be more likely to use other forms of care; people who know they are in the experimental group may experience *placebo effects*, and care providers may treat patients differently according to what group they are in. Masking (*blinding*) of both the recipients and providers of care is used to protect against performance bias.

Pilot study A small scale 'test' of the research instrument. For example, testing out (piloting) a new questionnaire with people who are similar to the population of the study, in order to highlight any problems or areas of concern, which can then be addressed before the full scale study begins.

Placebo Placebos are fake or inactive treatments received by participants allocated to the *control group* in a clinical trial which are indistinguishable from the active treatments being given in the experimental group. They are used so that participants are ignorant of their treatment allocation in order to be able to quantify the effect of the experimental treatment over and above any *placebo effect* due to receiving care or attention.

Placebo effect A beneficial (or adverse) effect produced by a placebo and not due to any property of the *placebo* itself.

Point estimate	A best single estimate (taken from research data) for the true value of a treatment effect or other measurement. For example, researchers in one clinical trial take their results as their best estimate of the real treatment effect – this is their estimate at their point in time. The precision or accuracy of the estimate is measured by a *confidence interval*. Another clinical trial of the same treatment will produce a different point estimate of treatment effect.
Positive likelihood ratio (LR+)	The positive likelihood ratio describes the probability of having a positive test result in the diseased population compared to that of a non-diseased population and corresponds to the ratio of the true positive rate divided by the false positive rate (sensitivity/1-specificity).
Positive predictive value (PPV)	The positive predictive value expresses the probability that a patient with a positive test result does have the condition.
Power	See *Statistical power*.
Power Doppler ultrasound (PDU	See *Ultrasound*
Prevalence	The total number of cases of a given disease in a specified population at a designated time.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses

	and other health care professionals, dentists, pharmacists and opticians. See comments Secondary Care
Primary Care Trust	A Primary Care Trust is an NHS organisation responsible for improving the health of local people, developing services provided by local GPs and their teams (called Primary Care) and making sure that other appropriate health services are in place to meet local people's needs.
Probability	How likely an event is to occur, e.g. how likely a treatment or intervention will alleviate a symptom.
Procalcitonin	Procalcitonin is a precursor of the hormone calcitonin, which is involved with calcium homeostasis, and is produced by the C-cells of the thyroid gland. It is there that procalcitonin is cleaved into calcitonin, katacalcin and a protein residue. It is not released into the blood stream of healthy individuals, therefore measurement of procalcitonin can be used as a marker of severe sepsis and generally grades well with the degree of sepsis.
Prognostic factor	Patient or disease characteristics, e.g. age or *co-morbidity*, which influence the course of the disease under study. In a randomised trial to compare two treatments, chance imbalances in *variables* (prognostic factors) that influence patient outcome are possible, especially if the size of the study is fairly small. In terms of analysis these

prognostic factors become *confounding factors*. See also *Prognostic marker*.

Prognostic marker A *prognostic factor* used to assign patients to categories for a specified purpose – e.g. for treatment, or as part of a clinical trial, according to the likely progression of the disease. For example, the purpose of randomisation in a clinical trial is to produce similar treatment groups with respect to important *prognostic factors*. This can often be achieved more efficiently if randomisation takes place within subgroups defined by the most important prognostic factors. Thus if age was very much related to patient outcome then separate randomisation schemes would be used for different age groups. This process is known as stratified random allocation.

Prophylaxis, antibiotic Use of antibiotics before, during, or after a diagnostic, therapeutic, or surgical procedure to prevent complications of infection.

Prospective study A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are *retrospective*.

Proteinuria The presence of proteins in the urine.

Protocol A plan or set of steps which defines appropriate action. A

research protocol sets out, in advance of carrying out the study, what question is to be answered and how information will be collected and analysed. Guideline implementation protocols set out how guideline recommendations will be used in practice by the NHS, both at national and local levels.

Publication bias Studies with statistically significant results are more likely to get published than those with non-significant results. *Meta-analyses* that are exclusively based on published literature may therefore produce biased results. This type of bias can be assessed by a *funnel plot*.

Public Health Laboratory Service Undertakes epidemiological surveillance, investigation and research of communicable disease and produces independent advice on the prevention and control of communicable disease. Merged with Communicable Disease Surveillance Centre.

P value If a study is done to compare two treatments then the P value is the probability of obtaining the results of that study, or something more extreme, if there really was no difference between treatments. (The assumption that there really is no difference between treatments is called the 'null hypothesis'.) Suppose the P-value was P=0.03. What this means is that if there really was no difference

between treatments then there would only be a 3% chance of getting the kind of results obtained. Since this chance seems quite low we should question the validity of the assumption that there really is no difference between treatments. We would conclude that there probably is a difference between treatments. By convention, where the value of P is below 0.05 (i.e. less than 5%) the result is seen as statistically significant. Where the value of P is 0.001 or less, the result is seen as highly significant. P values just tell us whether an effect can be regarded as statistically significant or not. In no way do they relate to how big the effect might be, for which we need the *confidence interval*.

Pyelonephritis See *acute pyelonephritis* and *chronic pyelonephritis*

Pyuria The production of urine which contains white blood cells.

Qualitative research Qualitative research is used to explore and understand people's beliefs, experiences, attitudes, behaviour and interactions. It generates non-numerical data, e.g. a patient's description of their pain rather than a measure of pain.. Analysis of qualitative data can and should be done using explicit, systematic, and reproducible methods (Greenhalgh , 1997) Qualitative research techniques such as *focus groups* and *in depth interviews* have been used

	in one-off projects commissioned by guideline development groups to find out more about the views and experiences of patients and carers.
Quality adjusted life years (QALYS)	A measure of health outcome which looks at both length of life and quality of life. QALYS are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighting each year with a quality of life score (on a zero to one scale). One QALY is equal to one year of life in perfect health, or two years at 50% health, and so on.
Quantitative research	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census which counts people and households.
Quasi experimental study	A study designed to test if a treatment or intervention has an effect on the course or outcome of disease. It differs from a *controlled clinical trial* and a *randomised controlled trial* in that: a) the assignment of patients to treatment and comparison groups is not done randomly, or patients are not given equal probabilities of selection, **or** b) the investigator does not have full control over the allocation and/or timing of the intervention, but nonetheless conducts the study as if it were an experiment, allocating

	subjects to treatment and comparison groups.
Random allocation or Randomisation	A method that uses the play of chance to assign participants to comparison groups in a research study, for example, by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual (or each unit in the case of *cluster randomisation*) being entered into a study has the same chance of receiving each of the possible interventions.
Randomised controlled trial (RCT)	A study to test a specific drug or other treatment in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. (Through randomisation, the groups should be similar in all aspects apart from the treatment they receive during the study.)
Receiver operator characteristic curve (ROC)	ROC curves are used to show the pattern of sensitivities and specificities observed when the performance of a test is evaluated at several different diagnostic thresholds. An ROC curve is a plot of sensitivity (ie. The true positive

	rate) verses 1-specificity (ie. The false positive rate). The overall diagnostic performance of a test can be judged by measuring the area under the ROC curve.
Reflux	See *Vesicoureteric reflux (VUR)*
Reflux nephropathy	A condition in which the kidneys are damaged in association with vesicoureteric reflux (backward flow of urine into the kidney) This can be either congenital, i.e. part of the same malformation as the VUR or acquired from an episode of acute pyelonephritis.
Relative risk (RR)	A summary measure which represents the ratio of the risk of a given event or outcome (e.g. an adverse reaction to the drug being tested) in one group of subjects compared to another group. When the 'risk' of the event is the same in the two groups the relative risk is 1. In a study comparing two treatments, a relative risk of 2 would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment. Relative risk is sometimes used as a synonym for *risk ratio*.
Reliability	Reliability refers to a method of measurement that consistently gives the same results. For example someone who has a high score on one occasion tends to have a high score if measured on another occasion very

	soon afterwards. With physical assessments it is possible for different clinicians to make independent assessments in quick succession – and if their assessments tend to agree then the method of assessment is said to be reliable.
Renal hypertension	High blood pressure due to kidney disease.
Renal National Service Framework (NSF)	Department of Health Policy on the management of chronic kidney disease and established renal failure.[2]
Retrospective study	A retrospective study deals with the past and does not involve studying future events. This contrasts with studies that are *prospective*.
Review	Summary of the main points and trends in the research literature on a specified topic. A review is considered non-systematic unless an extensive literature search has been carried out to ensure that all aspects of the topic are covered and an objective appraisal made of the quality of the studies.
Risk ratio	Ratio of the risk of an undesirable event or outcome occurring in a group of patients receiving experimental treatment compared with a comparison (control) group. The term *relative risk* is sometimes used as a synonym of risk ratio.

Royal Colleges	In the UK medical/nursing world the term royal colleges, as for example in 'The Royal College of…..', refers to organisations which usually combine an educational standards and examination role with the promotion of professional standards.
Sample	A part of the study's target population from which the subjects of the study will be recruited. If subjects are drawn in an unbiased way from a particular population, the results can be generalised from the sample to the population as a whole.
Sampling	Refers to the way participants are selected for inclusion in a study.
Sampling frame	A list or register of names which is used to recruit participants to a study.
Scottish Intercollegiate Guidelines Network (SIGN)	SIGN was established in 1993 to sponsor and support the development of evidence-based clinical guidelines for the NHS in Scotland.
Secondary care	Care provided by hospital based professionals (eg Hospital Care, Community Paediatrics/ outreach services)
Selection bias	Selection bias occurs when the method of selecting a population for a study alters the outcomes. Clues that selection bias has occurred are :

	the characteristics of the *sample differ* from those of the wider population from which the sample has been drawn OR there are systematic differences between comparison groups of patients in a study in terms of prognosis or disease progression unrelated to the treatment.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Semi-structured interview	Both structured and semi-structured interviews involve asking people pre-set questions. Unlike a structured interview (see below) a semi-structured interview allows the interviewer and the respondent flexibility to change the questions and the direction of the interview structured interview. The interviewer asks a number of open-ended questions, following up areas of interest in response to the information given by the respondent.
Sensitivity	In diagnostic testing, it refers to the chance of having a positive test result given that you have the disease. 100% sensitivity means that all those with the disease will test positive, but this is not the same the other way around. A patient could have a positive test result but not have the disease – this is called a 'false positive'. The sensitivity of

a test is also related to its 'negative predictive value' (true negatives) – a test with a sensitivity of 100% means that all those (or almost all those in very large studies) who get a negative test result do not have the disease. To fully judge the accuracy of a test, its *Specificity* must also be considered.

SIGN See *Scottish Intercollegiate Guidelines Network*

Single blind study A study in which either the subject (patient/participant) or the observer (clinician/investigator) is not aware of which treatment or intervention the subject is receiving.

Specific indication When a drug or a device has a specific remit to treat a specific condition and is not licensed for use in treating other conditions or diseases.

Specificity In diagnostic testing, it refers to the chance of having a negative test result given that you do not have the disease. 100% specificity means that all those without the disease will test negative, but this is not the same the other way around. A patient could have a negative test result yet still have the disease – this is called a 'false negative'. The specificity of a test is also related to its 'positive predictive value' (true positives) – a test with a specificity of 100% means that all those (or almost all those in very large studies) who get a positive test result

	definitely have the disease. To fully judge the accuracy of a test, its *Sensitivity* must also be considered.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data. 95% of a population will lie within 3 standard deviations either side of the mean.
Statistical power	The ability of a study to demonstrate an association or causal relationship between two *variables*, given that an association exists. For example, 80% power in a clinical trial means that the study has a 80% chance of ending up with a P value of less than 5% in a statistical test (i.e. a statistically significant treatment effect) if there really was an important difference (e.g. 10% versus 5% mortality) between treatments. If the statistical power of a study is low, the study results will be questionable (the study might have been too small to detect any differences). By convention, 80% is an acceptable level of power. See also *P value*.
Structured interview	A research technique where the interviewer controls the interview by adhering strictly to a questionnaire or interview schedule with pre-set questions.
Study checklist	A list of questions addressing the key aspects of the research methodology that must be in place if a study is to

	be accepted as valid. A different checklist is required for each study type. These checklists are used to ensure a degree of consistency in the way that studies are evaluated.
Study population	People who have been identified as the subjects of a study.
Study quality	See *Methodological quality*.
Study type	The kind of design used for a study. *Randomised controlled trial, case-control study, cohort study* are all examples of study types.
Subject	A person who takes part in an experiment or research study.
Summary receiver operator characteristic curve (SROC)	The summary receiver operating characteristic curve has been recommended to represent the performance of a diagnostic test, based on data from a meta-analysis
Suprapubic aspiration (SPA)	The collection of a urine sample by inserting a needle directly into the bladder through the anterior abdominal wall above the pubic bone.
Survey	A study in which information is systematically collected from people (usually from a sample within a defined population).
Systematic	Methodical, according to plan; not random.

Systematic error Errors may be systematic or random. Errors that are systematic are inherent in studies. Examples of errors are incorrect data measurements/ collection/ analyses caused by humans, machines, acts of God, or inappropriate acts of interpretation – eg over-diagnosis of UTI due to reliance on the Leucocyte test alone would be an error (but not a bias)

Systematic review A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a *meta-analysis*.

Systemic Involving the whole body.

Target population The people to whom guideline recommendations are intended to apply. Recommendations may be less valid if applied to a population with different characteristics from the participants in the research study – e.g. in terms of age, disease state, social background.

Tertiary centre A major medical centre providing complex treatments which receives referrals from both primary and secondary care. Sometimes called a tertiary referral centre. See also *Primary care* and *Secondary care*.

Triangulation Use of more than one research methods in combination; principally used as a check of validity. The more the

different methods produce similar results, the more valid the findings.

Triple blind study A study in which the statistical analysis is carried out without knowing which treatment patients received, in addition to the patients and investigators/clinicians being unaware which treatment patients were getting.

Trust A trust is an NHS organisation responsible for providing a group of healthcare services. An *acute trust* provides hospital services. A *mental health trust* provides most mental health services. A *primary care trust* buys hospital care on behalf of the local population, as well as being responsible for the provision of community health services.

Tumour Necrosis Factor - alpha Serum glycoprotein produced by activated macrophages and other mammalian mononuclear leukocytes. It has necrotizing activity against tumor cell lines and increases ability to reject tumor transplants. Also known as TNF-alpha, it is only 30% homologous to TNF-beta (lymphotoxin), but they share TNF receptors.

Ultrasound High frequency sound waves reflected off internal structures are reconstructed into images providing excellent anatomic information without the use of ionising radiation. There are no known hazards associated with

	ultrasound making it an ideal first line investigation of the renal tract in children. The use of *Doppler* ultrasound permits some functional information about the blood flow and perfusion of the kidneys. Power Doppler is a refinement of conventional Doppler ultrasound, and is very sensitive for assessing blood flow.
Urgency (urinary)	A strong, sudden need to urinate immediately.
Urinalysis	Examination of urine by chemical, physical, or microscopic means. Routine urinalysis usually includes performing chemical screening tests, determining specific gravity, observing any unusual colour or odour, screening for bacteriuria, and examining the sediment microscopically.
Urine culture	See *Culture*
Validity	Assessment of how well a tool or instrument measures what it is intended to measure. See also *External validity, Internal validity*.
Variable	A measurement that can vary within a study, e.g. the age of participants. Variability is present when differences can be seen between different people or within the same person over time, with respect to any characteristic or feature which can be assessed or measured.

Vesicoureteric reflux (VUR)	The passage of urine from the bladder back into a ureter and in higher grades of reflux, to the kidneys. Grade I: Ureter only Grade II: Ureter, pelvis an calyces; no dilatation, normal calyceal fornices Grade III: Mild or moderate dilatation and/or tortuosity of the ureter and mild or moderate dilatation of the renal pelvis. No or slight blunting of the fornices. Grade IV: Moderate dilatation and/or tortuosity of the ureter and moderate dilatation of the renal pelvis and calyces. Complete obliteration of the sharp angle of the fornicies but maintenance of the papillary impressions in the majority of calyces. Grade V: Gross dilatation and tortuosity of the ureter. Gross dilatation of the renal pelvis and calyces. The papillary impressions are no longer visible in the majority of calyces.[3]
Voiding cystourethrogram (VCUG)	See *Micturating cystourethrogram (MCUG)*
Voiding urosonography (VUS)	Involves the use of an echo-enhancing contrast agent that is introduced slowly into the bladder through a catheter. It is used to detect reflux. It has the advantage of not using

	ionising radiation, but the disadvantage that it does not provide anatomic detail of the urethra.
Weighted mean difference	A summary effect size measure for continuous data where studies that have measured the outcome on the same scale have been pooled.

1 Introduction

1.1 Urinary Tract Infection

In the past 30-50 years, the natural history of urinary tract infection (UTI) in children has changed, as a result of the introduction of antibiotics and improvements in healthcare. This change has contributed to uncertainty about the most appropriate and effective way to diagnose and treat UTI in children and whether or not investigations and follow up are justified.

UTI is a common bacterial infection causing illness in infants and children. It may be difficult to recognise UTI in children because the presenting symptoms and/or signs are non-specific, particularly in the youngest children. Urine collection and interpretation of urine tests in infants and toddlers are not easy and therefore it may not always be possible to unequivocally confirm the diagnosis.

Current Management involving imaging, prophylaxis and prolonged follow up has placed a heavy burden on NHS primary and secondary care resources, and is unpleasant for children and families, costly and not evidence-based. The aim of this guideline is to lead to more consistent clinical practice, by considering the effectiveness of investigations and treatment including surgical intervention. The importance of accurate diagnosis depends on the effectiveness of subsequent investigations and follow up in altering the outcome.

1.2 Aim of the guideline

Clinical guidelines have been defined as 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'.[4] The guideline has been developed with the aim of providing guidance on the following:

a) When to consider the diagnosis of UTI in sick and/or symptomatic infants and children who were previously healthy.
b) When and how to collect urine for the diagnosis of UTI in infants and children.
c) Which tests establish or exclude UTI as the cause of illness in infants and children
d) How to treat sick and/or symptomatic infants and children, including:
    - When to admit to hospital

- When to start treatment
- Which antibiotics to use
- What route of administration to use
- How long to treat

e) How and when to treat symptomatic re-infection.

f) When to use prophylactic antibiotics, which antibiotics to use and when to stop them.

g) When to use investigations to assess the structure and function of the urinary tract.

h) When to refer to secondary and tertiary care

i) When to offer surgical intervention

j) When to do long-term follow up.

k) What advice to give carers and parents, including what to do if another UTI occurs.

1.3 Areas outside of the remit of the guideline

a) Children with urinary catheters in situ

b) Children with neurogenic bladders

c) Children already known to have significant pre-existing uropathies

d) Children with underlying renal disease (for example, nephrotic syndrome).

e) Immunosupressed children

f) Infants and children in intensive care units.

g) Preventative measures or long-term management of sexually active girls with recurrent UTI.

1.4 For whom is the guideline intended?

This guideline is relevant to those who work in or use the National Health Service (NHS) in England and Wales. In particular:

a) All health care professional involved in providing care for children who have a UTI (including GPs, Nurses, Paediatricians, Nephrologists and Urologists)

b) Those responsible for commissioning and planning healthcare services, including primary care trust commissioners, Health Commission Wales commissioners, and public health and trust managers.

c) Children who have UTI and their families

A version of this guideline for children, young people, parents, carers and the public is available, entitled <Insert IFP Title>. It can be downloaded from the National Institute for Health and Clinical Excellence (NICE) website (www.nice.org.uk/insertcorrectaddress) or ordered via the NHS Response Line (0870 1555 455) quoting reference number <Insert Reference Number>.

1.5 Who has developed the guideline?

The guideline was developed by a multi-professional and lay working group (the Guideline Development Group or GDG) convened by the National Collaborating Centre for Women's and Children's Health (NCC-WCH). Membership is listed above.

Staff from the NCC-WCH provided methodological support for the guideline development process, undertook systematic searches, retrieval and appraisal of the evidence, health economics modelling and wrote successive drafts of the guideline.

All GDG members' interests were recorded on declaration form provided by NICE. The form covered consultancies, fee-paid work, shareholdings, fellowships, and support from the healthcare industry.

1.6 Other relevant documents

This guideline is intended to complement other existing and proposed works of relevance, including:

- Health Technology Appraisal, Clinical and cost-effectiveness of tests for the diagnosis and evaluation of urinary tract infection (UTI) in children: a systematic review and economic model (due for publication late 2006).
- NICE guidance. Fever in Children (expected publication June 2007).

1.7 Guideline Development Methodology

This guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in the NICE Technical Manual.[5]

Literature search strategy

Initial scoping searches were executed to identify relevant guidelines (local, national and international) produced by other development groups. The reference lists in these guidelines were checked against subsequent searches to identify missing evidence.

Relevant published evidence to inform the guideline development process and answer the clinical questions was identified by systematic search strategies. Additionally, stakeholder organisations were invited to submit evidence for consideration by the GDG provided it was relevant to the clinical questions and of equivalent or better quality that evidence identified by the search strategies.

Systematic searches to answer the clinical questions formulated and agreed by the GDG were executed using the following core databases via the OVID platform: Medline (1966 onwards), Cochrane Central Register of Controlled Trials (2nd Quarter 2006), Cochrane Database of Systematic Review (2nd Quarter 2006), Database of Abstracts of Reviews of Effects (2nd Quarter 2006). Embase (1980 onwards), and Cumulative Index to Nursing and Allied Health Literature (1982 onwards). Other databases, also via the OVID platform, utilised for specific

questions were PsycINFO (1967 onwards), and Allied and Complementary Medicine Database (Datastar, 1985 onwards).

Search strategies combined relevant controlled vocabulary and natural language in an effort to balance sensitivity and specificity. Unless advised by the GDG, searches were not date specific. Language restrictions were not applied to searches. Both generic and specially developed methodological search filters were used appropriately.

Searches to identify economic studies were undertaken using the above databases, and the NHS Economic Evaluations Database (NHS EED) produced by the Centre for Reviews and Dissemination at the University of York.

There was no systematic attempt to search grey literature (conferences, abstracts, theses and unpublished trials). Hand searching of journals not indexed on the databases was not undertaken.

At the end of the guideline development process searches were updated and re-executed, thereby including evidence published and included in the databases up to 1 June 2006. Any evidence published after this date was not included. This date should be considered the starting point for searching for new evidence for future updates to this guideline.

Further details of the search strategies, including the methodological filters employed, can be obtained from the NCC-WCH.

It was not possible to supply GDG members with original papers from which the technical team developed the systematic reviews. Evidence statements, translations and recommendations were based on these reviews. Additionally, the guideline is in draft form and the imperative to enter into consultation means the GDG feel the document is work in progress.

Synthesis of clinical effectiveness evidence

Evidence relating to clinical effectiveness was reviewed using established guides[5-12] and classified using the established hierarchical system shown in Table 1.1.[12] This system reflects the susceptibility to bias that is inherent in particular study designs.

The type of clinical question dictates the highest level of evidence that may be sought. In assessing the quality of the evidence, each study receives a quality rating coded as '++', '+' or '-'. For issues of therapy or treatment, the highest possible evidence level (EL) is a well-conducted systematic review or meta-analysis of randomised controlled trials (RCTs; EL=1++) or an individual RCT (EL=1+). Studies of poor quality are rated as '-'. Usually, studies rated as '-' should not be used as a basis for making a recommendation, but they can be

used to inform recommendations. For issues of prognosis, the highest possible level of evidence is a cohort study (EL=2-).

Table 1.1 Levels of evidence for intervention studies[9]

Level	Source of evidence
1++	▪ High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	▪ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	▪ Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	▪ High-quality systematic reviews of case-control or cohort studies ▪ High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	▪ Well-conducted case-control or cohort studies with a low risk of confounding , bias or chance and a moderate probability that the relationship is causal
2-	▪ Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	▪ Non-analytical studies (for example, case reports, case series)
4	▪ Expert opinion, formal consensus

For each clinical question, the highest available level of evidence was selected. Where appropriate, for example, if a systematic review, meta-analysis or RCT existed in relation to a question, studies of a weaker design were not included. Where systematic reviews, meta-analyses and RCTs did not exist, other appropriate experimental or observational studies were sought. For diagnostic tests, test evaluation studies examining the performance of the test were used if the efficacy of the test required, but where an evaluation of the effectiveness of the test in the clinical management of patients and the outcome of disease was required, evidence from RCTs or cohort studies was used.

The system described above covers studies of treatment effectiveness. However, it is less appropriate for studies reporting diagnostic tests of accuracy. In the absence of a validated ranking system for this type of test, NICE has developed a hierarchy for evidence of accuracy of diagnostic tests that takes into account the various factors likely to affect the validity of these studies (Table 1.2).[5]

Staff from the NCC-WCH provided methodological support for the guideline development process, undertook systematic searches, retrieved and appraised literature and wrote systematic reviews. The GDG appraised and edited the systematic reviews and generated evidence statements and recommendations based on their content.

Table 1.2 Levels of evidence for studies of the accuracy of diagnostics tests[5]

Level	Type of evidence
Ia	Systematic review (with homogeneity)* of level-1 studies†
Ib	Level-1 studies†
II	Level-2 studies‡
	Systematic reviews of level-2 studies
III	Level-3 studies§
	Systematic reviews of level-3 studies
IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'

*Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

†Level-1 studies are studies:

that use a blind comparison of the test with a validated reference standard (gold standard)

in a sample of patients that reflects the population to whom the test would apply.

‡Level-2 studies are studies that have only one of the following:

narrow population (the sample does not reflect the population to whom the test would apply)

use a poor reference standard (defined as that where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference')

the comparison between the test and reference standard is not blind

case-control studies

[§]Level-3 studies are studies that have at least two or three of the features listed above

For economic evaluations, no standard system of grading the quality of evidence exists. Economic evaluations that are included in the review have been assessed using a quality assessment checklist based on good practice in decision- analytic modelling.[13]

Evidence was synthesised qualitatively by summarising the content of identified papers in evidence tables and agreeing brief statements that accurately reflected the evidence. Quantitative synthesis (meta-analysis) was performed where appropriate.

Summary results and data are presented in the guideline text. More detailed results and data are presented in the accompanying evidence tables. Where possible, dichotomous outcomes are presented as relative risks (RRs) with 95% confidence intervals (CIs), and continuous outcomes are presented as mean differences with 95% CIs or standard deviations (SDs). Meta-analyses based on dichotomous outcomes are presented as pooled odds ratios (ORs) with 95% CIs,

and meta-analyses based on continuous outcomes are presented as weighted mean differences (WMDs) with 95% CIs.

Health economics

The aim of the economic input into the guideline was to inform the GDG of potential economic issues relating to UTI in children.

The health economist helped the GDG by identifying topics within the guideline that might benefit from economic analysis, reviewing the available economic evidence and, where necessary, conducting (or commissioning) economic analysis. Reviews of published health economic evidence are presented alongside the reviews of clinical evidence where appropriate. Where no published economic evidence was available to inform the GDG in their decision making, the health economist advised the GDG on the potential impact on resource use resulting from the recommendations made in the guideline.

Forming and grading recommendations

For each clinical question, recommendations were derived using, and explicitly linked to, the evidence that supported them. In the first instance, informal consensus methods were used by the GDG to agree evidence statements and recommendations. Shortly before the consultation period, formal consensus

methods were used to agree guideline recommendations (modified Delphi technique) and to select 5–10 key priorities for implementation (nominal group technique).

External review

This guideline has been developed in accordance with the NICE guideline development process. This has included giving registered stakeholder organisations the opportunity to comment on the scope of the guideline at the initial stage of development and on the evidence and recommendations at the concluding stage. The developers have carefully considered all of the comments during the consultation period by registered stakeholders and validation by NICE. After the consultation period, changes were made to the final document. A summary of these changes is presented in Appendix XXX.

Outcome measures used in the guideline

- Recurrent UTI
- Persistence of bacteriuria
- Presence of VUR
- Adverse events
- Health Economics
- The Guideline Development Group considered other outcomes as they were relevant to specific questions.

1.8 Schedule for updating the guideline

Clinical guidelines commissioned by NICE are published with a review date 4 years from date of publication. Reviewing may begin earlier than 4 years if significant evidence that affects guideline recommendations is identified sooner. The updated guideline will be available within 2 years of the start of the review process.

2 Summary of recommendations and practice algorithm

2.1 Key priorities for implementation (key recommendations)

Chapter 4.3

Neonates with any signs or symptoms (Table 4.3.2) should have a urine sample tested.

Children who are unable to communicate their symptoms and have two or more clinical signs or symptoms (Table 4.3.2) should have a urine sample tested. UTI should also be considered in children with unexplained persistent symptoms or signs.

Children who are able to communicate their symptoms and present with any of most common symptoms or signs or two or more less common symptoms or signs should have a urine sample tested.

Table 4.3.2 Presenting signs and symptoms in children with UTI

Age Groups	Most common → Least common		
Neonates	Fever Vomiting Lethargy Irritability	Poor feeding Failure to thrive	Abdominal pain Jaundice Haematuria Offensive urine

Children	Pre-verbal	Fever	Abdominal pain or abdominal/loin tenderness Vomiting Poor feeding	Lethargy Irritability Haematuria Offensive urine Failure to thrive
	Verbal	Frequency Dysuria	Dysfunctional voiding Changes to continence Abdominal/loin pain or tenderness	Fever Malaise Vomiting Haematuria Offensive urine Cloudy urine

Any child can present with septic shock secondary to UTI, although this is more common in infants.

Fever defined as >38°C

Chapter 4.5

Clean catch urine sample is the recommended method for urine collection.

If a clean catch urine sample is unobtainable:

- Other non-invasive methods, such as urine collection pads should be used. It is important to follow the manufacturers instructions in using urine collection pads.
- When it is not possible or practical to collect urine by non-invasive methods, catheter samples or SPA should be used.
- If SPA is required, ultrasound guidance should be used to demonstrate the presence of urine in the bladder before SPA is attempted. This procedure should only be done by appropriately trained clinicians.

Cotton wool balls, gauze and sanitary towels should not be used to collect urine in children.

In an acutely unwell child it is highly preferable that a urine sample is obtained, however, treatment should not be delayed if a urine sample is unobtainable.

Chapter 5.2

Systemically well children with urinary tract infection

- Treat with 3 days oral antibiotics. The choice of antibiotics should be directed by locally developed multi-disciplinary guidance.
- If the child is still unwell after 24-48 hours carers should be advised to return for review.
- Systemically well children who return for review and who have not improved should be reassessed. If an alternative diagnosis is not made a urine sample should be sent for culture to identify the presence of bacteria and determine antibiotic sensitivity. Severely ill children should be referred to secondary care.

Chapter 5.5.3

Prophylaxis should not be routinely recommended in children with UTI.

Chapter 6.7

Children who are systemically well only need ultrasound (within six weeks) if they are younger than six months of age or have had recurrent infection. No

other investigations are required for any child who is systemically well unless they have recurrent UTI and abnormality on ultrasound in which case late DMSA should be considered.

Children who are systemically unwell should be imaged according to the following tables.

Table 6.7.1 Infants aged 0 to 6 months

Test	Responds well to treatment	Severe or atypical UTI	Recurrent UTI
Early Ultrasound	N	Y	Y
Late ultrasound	Y (within 6 weeks)*	N	N
Early DMSA	N	N	N
Late DMSA	N	Y**	Y
MCUG	N	Y***	Y***

*If abnormal consider MCUG
**Late DMSA in children with severe or atypical illness and those who responded poorly to treatment is to assess the level of renal damage.
*** When MCUG is performed, prophylactic antibiotics should be given orally for 3 days with MCUG taking place on the second day

Table 6.7.2 Children 6 months to toilet trained

Test	Responds well to treatment	Severe or atypical UTI	Recurrent UTI
Early Ultrasound	N	Y	N
Late ultrasound	N	N	Y
Early DMSA	N	N	N
Late DMSA	N	Y	Y
MCUG	N	N*	N*

* While MCUG need not be performed routinely it should be considered if the following features are present:
- Poor urine flow
- Family history of VUR.
- Non E.coli infection
- Dilatation on ultrasound

Table 6.7.3 Children toilet trained and older

Test	Responds well to treatment	Severe or atypical UTI	Recurrent UTI
Early Ultrasound	N	Y*	N
Late ultrasound	N	N	Y
Early DMSA	N	N	N
Late DMSA	N	N	Y
MCUG	N	N	N

*Ultrasound in toilet-trained children should be performed with a full bladder with an estimate of bladder volume pre and post micturition.

Definitions

Atypical UTI: Still febrile after 48 hours of appropriate treatment, poor urine flow or non-E.coli

Recurrent UTI: Two or more episodes of UTI with systemic symptoms/signs or three or more episodes of UTI without systemic symptoms/signs.

Early ultrasound: During the acute episode.

Late ultrasound: Within 6 weeks

Early DMSA: During the acute illness

Late DMSA: Six month or more following the acute infection

MCUG: Prophylactic antibiotics should be given for 3 days with MCUG taking place on the second day.

2.2 Key priorities for research (key research recommendations)

Chapter 3.4 A well-designed cohort study investigating long-term outcomes including renal scarring and renal function of children with urinary tract infection should be conducted in the UK.

(Research question: What are the long term risks including renal scarring and renal function in children who have a urinary tract infection during childhood?)

Chapter 4.7 Further investigation of nitrite and leukocyte dipstick tests alone and in combination in an age stratified population are required to determine their accuracy in diagnosing UTI.

(Research question: What is the accuracy and effectiveness of nitrite and leukocyte esterase urine dipstick tests alone and in combination in children of different age groups?)

Chapter 5.5.3 Well designed randomized, double blinded, placebo controlled trials are required to determine the effectiveness of prophylactic antibiotics for preventing subsequent symptomatic UTIs and renal parenchymal defects in children.

(Research question: What is the effectiveness of antibiotic prophylaxis for preventing subsequent urinary tract infections and renal parenchymal defects in children?)

Chapter 7 Well designed randomised placebo controlled trials are required to determine how effective prophylaxis or various surgical procedures for the management of VUR are in preventing recurrent urinary infection or renal parenchymal defects.

(Research question: What is the effectiveness of surgical intervention or prophylaxis for vesicoureteric reflux in preventing recurrent urinary tract infections and renal parenchymal damage?)

2.3 Summary of recommendations

Chapter 4 – Diagnosis

Chapter 4.2 Predisposing factors

Women should be made aware that breast-feeding, among other benefits, is likely to offer protection against UTI in infants.

Chapter 4.3 Symptoms and signs

Neonates with any signs or symptoms (Table 4.3.2) should have a urine sample tested.

Children who are unable to communicate their symptoms and have two or more clinical signs or symptoms (Table 4.3.2) should have a urine sample tested. UTI should also be considered in children with unexplained persistent symptoms or signs.

Children who are able to communicate their symptoms and present with any of most common symptoms or signs or two or more less common symptoms or signs should have a urine sample tested.

Table 4.3.2 Presenting signs and symptoms in children with UTI

Age Groups		Most common → Least common		
Neonates		Fever Vomiting Lethargy Irritability	Poor feeding Failure to thrive	Abdominal pain Jaundice Haematuria Offensive urine
Children	Pre-verbal	Fever	Abdominal pain or abdominal/loin tenderness Vomiting Poor feeding	Lethargy Irritability Haematuria Offensive urine Failure to thrive
	Verbal	Frequency Dysuria	Dysfunctional voiding Changes to continence Abdominal/loin pain or tenderness	Fever Malaise Vomiting Haematuria Offensive urine Cloudy urine

Any child can present with septic shock secondary to UTI, although this is more common in infants.

Fever defined as >38°C

Chapter 4.4 Clinical features of UTI

Children with suspected UTI and the following the signs and symptoms should be defined as *Severely Ill*:

- Signs of dehydration

- Reduced activity/responsiveness
- Pale / mottled / ashen skin or blue
- Ill appearing

Children with suspected UTI, fever > 38^{O} C and at least one of the following features should be considered to be *Systemically Unwell:*
Loin or abdominal pain or tenderness, Vomiting, Irritability, Poor feeding, Chills and rigors

All other children with suspected UTI but no systemic features, should be considered to be *Systemically Well*.

Chapter 4.5 Urine collection

Clean catch urine sample is the recommended method for urine collection.

If a clean catch urine sample is unobtainable:

- Other non-invasive methods, such as urine collection pads should be used. It is important to follow the manufacturers instructions in using urine collection pads.
- When it is not possible or practical to collect urine by non-invasive methods, catheter samples or SPA should be used.
- If SPA is required, ultrasound guidance should be used to demonstrate the presence of urine in the bladder before SPA is attempted. This procedure should only be done by appropriately trained clinicians.

Cotton wool balls, gauze and sanitary towels should not be used to collect urine in children.

In an acutely unwell child it is highly preferable that a urine sample is obtained, however, treatment should not be delayed if a urine sample is unobtainable.

Chapter 4.6 Urine preservation

If urine cannot be cultured within four hours of collection the sample should be refrigerated or preserved with boric acid immediately on voiding.

When boric acid is used, manufacturers instructions should be followed to ensure correct specimen volume to avoid potential toxicity against bacteria in the specimen.

Chapter 4.7 Urine testing

In children over the age of three years, combined nitrite and leukocyte esterase dipstick tests are recommended to diagnose urinary tract infection.

In children under the age of three years urine should be sent for microscopy and culture to diagnose urinary tract infection.

Table 4.7.6.2 Dipstick results and UTI diagnosis

Urine Dipstick	Diagnosis
Nitrite and LE positive	UTI – treat with antibiotics
Nitrite positive and LE negative	Probable UTI – treat with antibiotics
Nitrite negative and LE positive	May or may not be UTI –

	management should be based on clinical judgment
Nitrite and LE negative	UTI Excluded – no antibiotic treatment

Dipstick testing is no less accurate than microscopy in children over the age of three years but is less operator dependent and less costly therefore Microscopy is not routinely recommended for diagnosing urinary tract infection in older children.

Urine samples should not be routinely sent for culture in children over the age of three years with first time urinary tract infection who have a urine dipstick which is negative or positive for both nitrite and leukocyte esterase.

Urine samples should be sent for culture in:

- Systemically unwell children of all ages
- All children under the age of three years
- Single positive result for nitrite or leukocyte esterase
- Recurrent urinary tract infection
- Children who do not respond to treatment within 24-48 hours
- When clinical symptoms and dipstick tests do not correlate

Laboratory investigations

CRP alone should not be used to differentiate upper from lower urinary tract infection in children.

Chapter 5 – Management

Chapter 5.2 Antibiotic treatment

These are based on initial stratification of patient groups based on severity of clinical presentation (see chapter 4).

Systemically well children with urinary tract infection

- Treat with 3 days oral antibiotics. The choice of antibiotics should be directed by locally developed multi-disciplinary guidance.
- If the child is still unwell after 24-48 hours carers should be advised to return for review.
- Systemically well children who return for review and who have not improved should be reassessed. If an alternative diagnosis is not made a urine sample should be sent for culture to identify the presence of bacteria and determine antibiotic sensitivity. Severely ill children should be referred to secondary care.

Systemically unwell children with urinary tract infection

- Consider referral to secondary care setting
- Treat with 10 to 14 days oral antibiotic treatment

If oral antibiotics are not tolerated and if the child is severely unwell, the following options are alternatives.

- 2-4 days IV antibiotic treatment followed by oral antibiotics for over 8 to 10 days to a total duration of 10 days

In infants and children who receive (aminoglycoside) gentamicin or amikacin, once daily dosing is recommended.

In the rare circumstances where oral or IV treatment are not possible, IM treatment should be considered.

Children who are systemically unwell and who do not respond to oral, IV or IM antibiotics within 24 - 48 hours should have a repeat urine culture to identify the causative organism and the antibiotic sensitivity if an alternative diagnosis is not made.

Chapter 5.3 Antibiotic treatment for asymptomatic bacteriuria

Asymptomatic bacteriuria in children should not be treated with antibiotics.

Chapter 5.5.2 Non-antibiotic strategies for preventing recurrence

Dysfunctional elimination syndromes and constipation should be addressed in children who have had a UTI.

Children who have had a UTI should be encouraged to drink an adequate amount.

Parents and carers should be advised to prevent children from delaying voiding by ensuring ready access to clean toilets when required at all times.

Chapter 5.5.3 Antibiotic prophylaxis

Antibiotic prophylaxis should not be routinely recommended in children with urinary tract infection.

Chapter 6 – Imaging

Chapter 6.2 Evaluation of the structure of the urinary tract

In all children with severe or atypical illness who do not respond to treatment within 48 hours, early ultrasound scan is recommended to identify structural abnormalities of the urinary tract. (Table 6.7.1 – 6.7.3)

In infants aged 0 to 6 months, late ultrasound (within 6 weeks) should be carried out following the first simple urinary tract infection. (Table 6.7.1 – 6.7.3)

In children over 6 months of age with simple first time UTI that responds to treatment, routine ultrasound is not recommended. (Table 6.7.1 – 6.7.3)

Chapter 6.3 Detecting vesicoureteric reflux

Routine imaging to identify vesicoureteric reflux is not recommended in children who have had a urinary tract infection, except in specific circumstances outlined in the tables. (Table 6.7.1 – 6.7.3)

When imaging is required to detect reflux in pre toilet trained boys, an MCUG is recommended so that the urethra is also imaged. In girls cystosonography is a valid alternative.

Chapter 6.5 Detecting renal parenchymal defects

A DMSA scan 6 months following the acute infection should be used to detect renal parenchymal defects as recommended. (Table 6.7.1 – 6.7.3)

If the child has a subsequent UTI while awaiting DMSA the timing of the DMSA should be reviewed.

IVU should not be used routinely to detect renal parenchymal defects in children who have had a UTI.

Chapter 6.6 Localistaion of infection

The routine use of imaging in the localisation of a urinary tract infection is not recommended.

In the rare instances where it is clinically important to confirm or exclude upper tract infection a DMSA scan is recommended.

If ultrasound is being performed during the acute infection to identify structural abnormalities the power doppler function should be used as it may provide additional information about renal parenchymal involvement.

Chapter 6.7 Recommendations for routine imaging

Children who are systemically well only need ultrasound (within six weeks) if they are younger than six months of age or have had recurrent infection. No other investigations are required for any child who is systemically well unless they have recurrent UTI and abnormality on ultrasound in which case late DMSA should be considered.

Children who are systemically unwell should be imaged according to the following tables.

Table 6.7.1 Infants aged 0 to 6 months

Test	Responds well to treatment	Severe or atypical UTI	Recurrent UTI
Early Ultrasound	N	Y	Y
Late ultrasound	Y (within 6 weeks)*	N	N
Early DMSA	N	N	N
Late DMSA	N	Y**	Y
MCUG	N	Y***	Y***

*If abnormal consider MCUG

**Late DMSA in children with severe or atypical illness and those who responded poorly to treatment is to assess the level of renal damage.

*** When MCUG is performed, prophylactic antibiotics should be given orally for 3 days with MCUG taking place on the second day

Table 6.7.2 Children 6 months to toilet trained

Test	Responds well to treatment	Severe or atypical UTI	Recurrent UTI
Early Ultrasound	N	Y	N
Late ultrasound	N	N	Y
Early DMSA	N	N	N
Late DMSA	N	Y	Y
MCUG	N	N*	N*

* While MCUG need not be performed routinely it should be considered if the following features are present:

- Poor urine flow
- Family history of VUR.
- Non E.coli infection
- Dilatation on ultrasound

Table 6.7.3 Children toilet trained and older

Test	Responds well to treatment	Severe or atypical UTI	Recurrent UTI
Early Ultrasound	N	Y*	N
Late ultrasound	N	N	Y
Early DMSA	N	N	N
Late DMSA	N	N	Y
MCUG	N	N	N

*Ultrasound in toilet-trained children should be performed with a full bladder with an estimate of bladder volume pre and post micturition.

Definitions

Atypical UTI: Still febrile after 48 hours of appropriate treatment, poor urine flow or non-*E.coli*

Recurrent UTI: Two or more episodes of UTI with systemic symptoms/signs or three or more episodes of UTI without systemic symptoms/signs.

Early ultrasound: During the acute episode.

Late ultrasound: Within 6 weeks

Early DMSA: During the acute illness

Late DMSA: Six month or more following the acute infection

MCUG: Prophylactic antibiotics should be given for 3 days with MCUG taking place on the second day.

Chapter 7 – Surgical Intervention

Surgical management of reflux with or without urinary tract infection is not routinely recommended.

Chapter 8 – Follow up

Children who do not undergo imaging investigations should not routinely be followed up.

Parents/carers should be informed of the results of the investigations in writing.

When results are normal, an outpatient appointment is not necessarily required.

Children who have recurrent urinary tract infections or abnormal imaging investigations should be seen by a paediatric specialist. Follow up should include height, weight, blood pressure and routine testing for proteinuria.

Children who have bilateral renal abnormalities, impaired kidney function, raised blood pressure and/or proteinuria should receive monitoring and appropriate management by a specialist to slow the progression of chronic kidney disease.

Children who are asymptomatic following an episode of urinary tract infection should not routinely have their urine re-tested for infection.

Asymptomatic bacteriuria is not an indication for follow up.

Chapter 9 – Advice

Healthcare Professionals should ensure that when a child or young person has been identified as having a possible urinary tract infection they are given appropriate information about the need for treatment, the importance of following any course of treatment through and advice around prevention

Healthcare professionals should ensure that children and young people, parents and carers, are aware of the possibility of a urinary tract infection reoccurring and that they should seek prompt treatment for any suspected re-infection.

Healthcare professional should give advice/information on:

- Prompt recognition of symptoms & urine collection and testing
- Appropriate treatment options

- Prevention
- The nature of and reason for any urinary tract investigation
- Prognosis

2.4 Research recommendations

Headings should be done in 'Guideline Text + Bold'

Any text should be in 'Guideline Text'. With any bullet points in

Guideline Text + Bullet

Chapter 3

Chapter 3.4 Epidemiology

A well-designed cohort study investigating long-term outcomes including renal scarring and renal function of children with urinary tract infection should be conducted in the UK.

Chapter 4

Chapter 4.2 Predisposing factors

More studies with adequate sample sizes are needed to evaluate the effectiveness of breastfeeding, nappies and hygiene in preventing childhood UTI.

Chapter 4.3 Symptoms and signs

Combined population based studies in primary and secondary care, with larger sample sizes are needed to evaluate the association between signs and symptoms and UTI.

Chapter 4.7 Urine testing

Further investigation of nitrite and leukocyte dipstick tests alone and in combination in an age stratified population are required to determine their accuracy in diagnosing urinary tract infection.

Further research is needed to evaluate the effectiveness of biochemical tests for low urinary glucose for diagnosing urinary tract infection in children.

Sysmex system gave a high NPV (98%) compared to dipstick tests and bacterial culture. Further evaluation of this system and the variety of selective criteria for performing the analysis is appropriate.

Chapter 4.8 Laboratory investigations

Further research is needed to evaluate the effectiveness of procalcitonin and other inflammatory markers in localising UTI.

Chapter 5.5.3 Antibiotic prophylaxis

Well designed randomized, double blinded, placebo controlled trials are required to determine the effectiveness of prophylactic antibiotics for preventing subsequent symptomatic UTIs and renal parenchymal defects in children.

Chapter 6.5 Detecting renal parenchymal defects

MRI appears to be an accurate method of detecting renal parenchymal defects however evidence is limited. Further studies investigating its diagnostic accuracy and cost-effectiveness are required.

Chapter 6.6 Localisation of infection

Further research on MRI for localising UTI could be considered.

2.5 Algorithm

3 Background

3.1 Introduction

Urine infection is one of the commonest bacterial infections.[14] In childhood it has special significance because of its variable presentation, often without urinary symptoms, difficulty with urine collection in infants and toddlers and consequently difficulty in making the diagnosis.[15] The commonest age for the first UTI in boys is during the first 6 months of life while girls are affected more often after 6 months of age and are more prone to recurrent infection.[16] There is an association with underlying congenital renal anomalies, particularly vesicoureteric reflux (VUR) and concern that infections treated late or inadequately may damage the kidney causing chronic pyelonephritis.[17] Because of the strong association with VUR these renal lesions have been described as reflux nephropathy.

The clinical spectrum of UTI in childhood includes non-specific illness with fever without urinary symptoms seen most often in infants as well as typical urinary symptoms of upper and lower tract infection similar to those seen in adults. The lack of urinary symptoms in infants and young children before they are old enough to communicate or are toilet trained may have contributed to under-diagnosis of this problem for many years. Untreated infection is likely either to resolve or to become asymptomatic after a period of time. Asymptomatic bacteriuria is common in male infants and school aged girls.

Examination of the early literature and various case reports, in comparison with recent literature, reveals that there has indeed been an improvement in the outlook for children with UTI and associated underlying urological and renal anomalies.[18] One paper described a large series of patients at post mortem who had chronic infection and scarred kidneys. They described their clinical course with recurrent episodes of acute pyelonephritis, renal failure, hypertension and proteinuria. They also described the typical appearance of chronic pyelonephritis seen at post mortem.

Other reports describe UTI in infants who were seriously ill with septicaemia and even deaths due to acute pyelonephritis.

The early literature has been confused by a lack of clarity between acute pyelonephritis and chronic pyelonephritis. Acute pyelonephritis is the term used to describe acute inflammation of the kidney during an acute bacterial urinary tract infection whereas chronic pyelonephritis represents the permanent renal damage with fibrosis that follows one or more episodes of acute infection. More recently, the term reflux nephropathy has been used as an alternative to chronic pyelonephritis to represent the observation that the majority of cases of chronic pyelonephritis were associated with VUR.

Over the past 30 years it has become clear that not all small kidneys are small as a result of acquired reflux nephropathy and that some kidneys recognised following UTI and associated with VUR are congenital dysplastic kidneys [19] In clinical practice it is not usually possible to distinguish between these two

causes of small kidneys which look very similar on routine imaging tests and both of which are often associated with VUR and UTI.

It is likely that the advent of antibiotics in the 1940s and the emergence of paediatrics as a specialty, with recognition that children and babies had their own spectrum of illness and treatment requirements have both contributed significantly to the improved outlook for children with UTI. It is possible that the improvement in outlook is more to do with the general improvement in care and fewer delays in treatment than the specific benefits of current management strategies.

The area that has been of particular concern to paediatricians is the observation that some children with recurrent UTI have gone on to develop progressive renal scarring, which in turn has resulted in severe hypertension, renal impairment, complicated pregnancies and renal failure.[20] Although cases have often been identified late, with bilateral renal scarring, few cases have been observed to progress from normal kidneys to renal failure. One study which looked at new scars identified 86 cases from several countries over a long time period. Characteristics of the cases with progressive scarring included recurrent UTI, VUR, delays in diagnosis, treatment, and imaging, inadequate supervision, and social difficulties[21] and a further series with similar characteristics in 1994.[22]

Knowledge that some children develop long term renal damage following one or more episodes of acute pyelonephritis has been at the heart of the

strategies used in management of UTI in childhood for over 30 years. These strategies have been concerned with imaging the urinary tract to exclude obstruction and identify VUR and other congenital anomalies as well as renal imaging to identify renal scarring.[23] However there was no proof that carrying out imaging tests after a child or infant has recovered from an illness is of any benefit to the child and clearly tests are inconvenient, uncomfortable and sometimes have risks attached.

Over the past 40 years strategies have been developed to attempt to reduce the risk of acquired renal damage based on emerging experience and knowledge, animal experiments and numerous anecdotal case series. The hypothesis was that the results of imaging tests informed subsequent management and that the management strategies were effective in preventing acquired renal damage, reflux nephropathy, or chronic pyelonephritis associated with VUR and UTI.

In addition to clinical observation, practice was influenced by animal experiments by Ransley and Risdon[24] who demonstrated that in the presence of VUR and UTI contrast and infected urine could enter the renal parenchyma in a retrograde direction via collecting ducts opening into compound papillae and cause scarring in the corresponding segments of renal cortex draining into these ducts. They demonstrated how the first infection could be devastating to the renal parenchyma of the mini-pig, early antibiotic treatment could prevent or attenuate the renal scarring and described a hypothetical

process whereby progression of scarring might evolve following the first insult as a result of further infections.

These animal studies tended to reinforce the importance of prompt diagnosis and treatment of the first infection as well as the importance of recognising and treating recurrent infection, particularly recurrent acute pyelonephritis.

From a clinical perspective, the two strategies that were considered to be most important for the prevention of progression of scarring were firstly, re-implantation of the ureter and later, long term low dose prophylaxis.

Relatively little emphasis has been placed on improving the primary diagnosis of the first UTI in infancy and early childhood in primary care where urine collection is particularly difficult. A study in the North of England showed that when a model of appropriate education was combined with prompt diagnosis and access to a nurse led UTI service, the pick up rate of children appropriately diagnosed with UTI was four times that of the control group.[25] However, this might be a very important part of preventing new renal scarring. It is logical to expect that early diagnosis and prompt treatment of the first and subsequent infections will be more effective in preventing the acquisition of renal scarring than an ultrasound or other more invasive imaging tests carried out after the child has recovered from the acute episode. It is clearly irrational to expect that any imaging test, carried out in a healthy child, will prevent the acquisition of scarring unless the subsequent management dictated by the

outcome of the test is more effective than treating infections promptly and effectively whenever they occur.

Since 1991 many paediatricians and some general practitioners have adopted the guidance of the Working Group of the Research Unit of the Royal College of Physicians who produced an opinion based consensus statement on the diagnosis and management of UTI in childhood.[26] These guidelines advocate that UTI should be considered in every child with a fever or urinary symptoms, that the diagnosis should be confirmed by culture of a urine sample and that, following treatment of the acute illness, infants and children under 7 Should receive prophylactic antibiotics until imaging tests have been completed. For paediatricians who previously grappled with an array of management proposals, suggested by various experts, with greater or numbers of imaging tests linked to surgery or prophylaxis, this authoritative document was most welcome and reasonably clear.

The imaging tests proposed were an ultrasound for all children, a late DMSA scan for all infants and children under 7 years and a MCUG for children under 1 year. This advice imposed a huge burden on local radiology departments as well as a burden on individual patients from these invasive tests. However, the yield of information on preventable long term renal damage was relatively poor and there was no evidence that doing these tests significantly altered the long term prognosis. In some cases children and their families found the burden of the imaging and follow up far exceeded the burden from a relatively

straightforward and short illness. The psychological trauma of imaging tests, particularly those involving catheterisation are well known. [24]

For children over 6 months and for children with minor symptoms or straight forward cases of acute pyelonephritis the results of ultrasound were largely normal, or where minor anomalies were detected, these had little impact on management. DMSA scans showed evidence of renal scarring in 22% of children admitted to hospital but only 11% overall and 1% for children not ill enough to be admitted to hospital.[27] VUR was detected in a third of cases as expected from the literature.[28] Children with renal anomalies and VUR were generally advised to continue to take long term low dose prophylaxis for two or more years, or in a few units, until VUR had been shown to resolve on repeat examination.

One of the important points made in the 1991 guideline was that infants in primary care were at high risk of UTI and that this diagnosis should be considered in all babies with a fever for over 24 hours without obvious cause. Although this was clearly stated there was no mechanism for getting this information to GPs and little evidence that the diagnosis of UTI in primary care improved in pre-toilet trained infants and toddlers. It was clear that GPs found this diagnosis difficult to make.[29]

One effect of the guideline was that practice in secondary care became more consistent and paediatricians were particularly assiduous in following the guidance on imaging. This enabled audit of the outcome of the imaging

strategy. Over time it has become clear that for the vast majority of children receiving an ultrasound scan the result is normal and even when anomalies are detected they have relatively little impact on management. The exception is for early ultrasound in children with severe illness, usually under 6 months, in whom obstruction is sometimes detected. [27;28]

The use of prophylactic antibiotics was based on the hypothesis that a small nightly dose of trimethoprim or nitrofurantioin will sterilize the residual bladder urine and eliminate any bacteria ascending the urethra, thus maintaining sterile urine, preventing recurrent symptomatic infection and renal scarring.

Since 1991 large numbers of children with relatively trivial illness have been given prophylaxis for relatively long periods of time without clear benefits or any indication of how long this should continue. This practice has the potential for unwanted side effects and needs careful thought. For the child and family it encourages an illness culture, making the child different from others because of medication and hospital visits. There is an increased risk of colonisation of the child with resistant organisms, making any subsequent infection less easy to treat and for the community at large it increases the overall rate of resistant organisms.

If renal scarring is acquired, and there are numerous case reports as well as animal studies to support this[30] then it may be equally effective if not more effective to concentrate resources on the early recognition of infants and children at risk of UTI, early diagnosis and prompt treatment of likely cases of

UTI with antibiotics. It is illogical to carry out extensive investigation of the urinary tract of otherwise healthy children after a single, simple UTI.

Benefits from the interventions recommended following imaging such as prophylactic antibiotics and re-implantation of the ureter have been based on hypothesis and anecdote. Additional imaging at follow up adds further to the burden to the patient and family as well as the radiology department without bringing any certainty of benefit.[24;31]

Focal renal scarring typical of chronic pyelonephritis is characterised by wedge shaped focal areas of scarring with fibrosis with overlying depression of the renal surface and linked to a distorted and mis-shapen renal calyx. These lesions can be recognised at post mortem or following nephrectemy and have a typical appearance at microscopy with areas of fibrosis, destruction of the normal glomerular and tubular architecture and an infiltrate of lymphocytes. This is distinctly different from the appearances of congenital renal dysplasia.

However in the usual clinical situation when children undergo imaging tests it is not always possible to distinguish between small kidneys with several focal scars as a result of chronic pyelonephritis and congenital renal dysplasia.

During life, views of the kidney are made using imaging such as renal ultrasound or DMSA scanning and in previous era the IVP was the principal imaging investigation for the kidney. On IVP chronic pyelonephritic scars

showed a characteristic appearance that closely mimicked the lesions seen by the pathologist. Ultrasound and DMSA are less precise although less invasive tests. They are able to demonstrate renal parenchymal defects but it is not possible to ascertain with any certainty whether they are congenital or acquired. Some patients have extensive renal scarring with a small smooth or irregular kidney. Some of these small kidneys are due to acquired renal scarring but others are due to congenital renal dysplasia.[19]

Over the past 20 years there has been a significant change in the choice and availability of imaging techniques used. Ultrasound has been popular as it provides information about the urinary tract without pain or radiation although the impact on management is small except where obstruction is suspected. Isotope scans have provided a range of tests useful for identifying renal parenchymal defects and VUR by direct and indirect techniques. However many of the studies that identified the relationship between UTI, renal scarring and VUR were based on IVP and MCUG. This makes interpretation of long term follow up studies more difficult and the significance of renal parenchymal defects identified using modern techniques less certain.

One difficulty for establishing the diagnosis relates to the way in which the colony count has been developed as a diagnostic tool and is interpreted in the laboratory. The concept was originally developed by Kass in 1956[32] The importance of a count of greater than 10^5 was derived from the need in his prospective studies to exclude all patients who did not have good evidence of bacteria in the urine. His studies were carried out on asymptomatic women

who did not require treatment for illness. In sick infants it is clear that a similar level is often but not always achieved. There is a danger that UTI associated with lower counts will be overlooked unless special steps are taken to obtain very clean urine samples by invasive methods and report all growth. In recent years much emphasis was attached to obtaining reasonable proof of a UTI because the majority of children were then subjected to imaging investigations some of which were quite invasive. However if these investigations are not necessary or helpful there is less need to be so accurate in diagnosing UTI in every case.

Methods of urine collection in early childhood are quite different from the methods used in older children and adults. There is a high risk of contamination of samples collected before children are toilet trained particularly if bags are used. Pads are more convenient and comfortable for most children. One significant problem in the small child is that many infant girls flush their vagina with urine when they pass urine and most infant boys flush their prepuce. The urine collected is thus very often contaminated and this cannot easily be altered by any of the non-invasive testing methods. After toilet training many children are able to produce reasonably good quality clean catch samples.

As it is widely believed that UTI in early childhood and infancy in under-diagnosed in primary care in the UK it has been difficult to get accurate population statistics for this age group and thus the true size of the problem is unknown. In some countries in northern Europe with different health care

arrangements for children are likely to provide more accurate results. In the North East a nurse led programme using a combination of education and support has produced a marked change in practice and the incidence of cases in early childhood is very close to the incidence in Sweden giving a lifetime risk of UTI in childhood 3% for boys and 12% for girls.[25]

In 2000 The HTA commissioned a review of the tests used for diagnosing and imaging UTI in childhood. This has provided a valuable source of evidence based information for this guideline. The analysis was largely confined to an assessment of the performance of one test compared to another test and there is no evidence to show whether or not any of these tests made any difference to the outcome for the patient. Thus the information available is not generally relevant to this guideline.

This guideline is concerned with the diagnosis and management of acute symptomatic and asymptomatic UTI in children not known to have significant underlying uropathy. It aims to provide sufficient information to enable diagnosis and treatment of UTI in infants and children of all ages and to give guidance on the benefits and drawbacks of any additional interventions after treatment of the acute infection. It also aims to provide sufficient advice to enable the very small number of children with progressive CKD to be identified and offered support in accordance with the aims of the National Service Framework (NSF) for renal services.[2] This document specifically recommends that children and young people who may have UTI should have

an accurate diagnosis and prompt treatment as well as sufficient investigation to identify structural defects and prevent scarring.

3.2 Defining UTI

A urinary tract infection is defined in this guideline by a combination of clinical features and bacteria in the urine.

Asymptomatic Bacteriuria (also known as occult or covert bacteriuria) is defined as the presence of bacteria in the urine without symptoms. Asymptomatic bacteriuria is not regarded as a urinary tract infection.

3.3 Epidemiology

3.4 Epidemiology

3.4.1 Introduction

This epidemiology section aims to provide basic epidemiological data on incidence and prevalence of UTI and associated renal anomalies relevant to management of UTI discussed in this guideline.

3.4.2 Population Statistics

Researchers have calculated rates of UTI according to annual incidence, cumulative incidence, prevalence, and incidence in cohorts or selected groups. Some authors also quote related rates, for example referral rates, diagnostic rates.

Annual incidence rates of childhood UTI can provide information on the frequency of disease, and workload (for example, the burden of investigation for first-time UTI)

The cumulative incidence of childhood UTI is a useful measure of risk, as clinical complications, for example renal failure, may happen many years after the initial event. These rates are usually estimates obtained by combining annual incidence rates for different age ranges of children.

Prevalence data is a measure of choice for chronic disease, but isn't suitable for an acute illness such as UTI. Prevalence data reported in this section relate to the presence of asymptomatic bacteriuria.

Incidence data is often presented for specific cohorts of children or groups of children sharing a common characteristic, for example all admissions, all febrile UTIs, or attending a clinic. Subsequent analysis can be subject to unpredictable bias.

When all children with first-time UTI are referred (as in the UK), referral rates can be used as a proxy for incidence and cumulative incidence rates, if case-finding is comprehensive and reliable.

Diagnostic rates are another measure, which can approximate to incidence. They can use clinical, laboratory, or near-patient testing. Some studies have used these rates to give a range of incidence.

3.4.3 Incidence

An early study in Sweden suggested that 3% girls and 1.1% of boys had UTIs by the age of 11.[16] Later studies, however, indicate that the population incidence of symptomatic UTI in developed countries is likely to be higher than previously recognised.

Figures from Sweden, whilst obtained retrospectively, are likely to be an accurate picture of the incidence of UTI before the age of 2. These show that in Sweden , with a tradition of research, that UTI occurs in a minimum of 2.1% girls and 2.2% boys before the age of 2. These figures are based on the confirmation of a UTI by a positive culture (>10^5cfu/ ml) and a positive nitrite test,. Up to a further 0.5% might have had a UTI; their rates of complications matched those with firmer diagnoses rather than population norms, suggesting that generally, they had valid diagnoses. The rates in most other Regions were less than Region 2, which suggests an influence from education and vigilance.[33]

In an area of the UK, where similar enthusiasm for diagnosis occurs, a population-based study (data collected for 4 years) suggested that 11.3% of

girls and 3.6% of boys will have had a UTI by the age of 16. The referral rate formed the basis for these figures, though 15% had no microbiological confirmation of the diagnosis.[34]

A study conducted in Sweden reported the cumulative incidence of UTI in children aged up until the age of seven years using a questionnaire about urinary symptoms at a school entrance health examination. Previous UTIs were reported in 274 children, however, after checking original records UTIs were confirmed in 145/1719 (8.4%) of girls and 32/1834 (1.7%) of boys.[35]

A small study in English General Practice (14 UTIs over 2 years in 2789 children) using strict diagnostic criteria, found the annual incidence of first time UTI to be 0.31% for girls and 0.17% for boys. This suggests a Cumulative Incidence of 5% girls and 2.7% boys during childhood, however this small population is unlikely to be representative. Only 9% children whose differential diagnosis included UTI had positive samples.[36] 6/14 had history suggesting previous UTI and all but 1 relapsed following treatment.

A study from Sweden of children under 10 reported that 59% of boys have their first UTI detected under the age of 1, but only 19% of girls.[37]

A study of UK and Finnish hospital discharge data reported a doubling of rates in boys and girls under and over 4 years between 1987 and 1993 in the UK. In Finland, rates in girls reduced between 1979 and 1994 but remained the same for boys. These results suggest that vigilance and medical management influence incidence rates.[38]

Discussion

An accurate cumulative incidence rate for UTI during childhood is difficult. Studies use a variety of methods and cut-off points, and enthusiasm for diagnosis has a significant effect on reported rates.

It is likely that around 1/10 girls and 1/30 boys will have had a UTI by the age of 16. Cumulative incidence figures are most accurate for infants: 2.1% of girls and 2.2% of boys will have had a UTI before the age of 2.

Boys have a greater incidence of UTI in the neonatal period and early infancy. Depending on the study viewed, girls overtake boys in the incidence of UTI somewhere between 3 and 6 months of age. About 1/2 boys will present for the first-time before age 1, but 4/5 girls present at a later age.

Evidence is limited to one study, but 1/10 children with UTI like symptoms are found to have positive cultures in Primary Care.

3.4.4 Acute Pyelonephritis

This section considers the incidence of acute infection. Scarring, Reflux Nephropathy and Chronic Pyelonephritis are terms, and are used to indicate long-term damage to a kidney as a result of infection.

Studies of acute pyelonephritis use various combinations of signs, symptoms and laboratory tests to establish a diagnosis.

In a study conducted in Sweden, 47/1719 (2.7%) girls and 19/1834(1%) boys had an episode of pyelonephritis by the age of seven. As a proportion of those with a history of UTI, this equated to 47/145 (32%) of girls and 19/32 (59%) of boys.[35]

The annual incidence of pyelonephritis in a study in South Korea based on insurance claim diagnosis was 0.15% girls and 0.07% boys. Only 1/7 were

treated in hospital.[39] In Italy[40] a study evaluated data from a children's health referral centre in the Trieste region of Italy and found annual rates of 0.13% in girls and 0.02% in boys and in the USA[41] hospital discharge data showed rates of 0.09% in girls and 0.01% in boys. Serious bacteraemic UTI is rare: 1.5/100,000 children/yr in a study from Finland. 66% of these were under 3 months and 88% under a year. Boys were affected almost twice as much as girls, though male predominance decreased with age.[42]

Discussion

On a population basis, acute pyelonephritis is a more common diagnosis in girls, but UTIs as a whole are more common than in boys. Obtaining annual incidence figures for the UK is difficult, but in other countries studies showed good agreement on a rate of approximately 1/1,000 girls per year. The figures for boys are less certain, with a range of 1/10,000 to 7/10,000.

Boys are more likely than girls to have an episode of acute pyelonephritis if they have a history of UTI. (1/2 boys v 1/3 girls). This is probably caused by differences between boys and girls in the age at presentation, rather than as a result of any other underlying predisposition. Girls also experience more recurrences than boys and differences in annual and cumulative incidence rates often reflect recurrences rather than first time UTIs.

Serious bacteraemic illness from UTI is quite rare. Around 9/10 children presenting in this way will be under one year old, most under 3 months, and pyelonephritis itself is not common. Estimates of bacteraemic UTI are approximately 1/150 episodes of pyelonephritis in girls will be bacteraemic but 1/10 or possibly more episodes will be bacteraemic in boys.

3.4.5 Demographic Characteristics

Two studies in children with febrile UTI, investigated characteristics associated with presentation. Further details on predisposing factors can be found in chapter 4.2.

In two studies from the USA, higher rates of febrile UTI were noted in girls, uncircumcised boys and those with a previous history of UTI. Lower levels were noted in children of Afro- American descent.[43;44]

A study quoted in the Section 1.2.1 noted a cyclical pattern in incidence over two consecutive years with June the commonest, and December the least common month for childhood UTI.[33] A study of pyelonephritis in South Korea also showed a summer peak.[39]

Discussion

Although certain groups have higher incidences of UTI, there are no clear reasons for these rates.

Two studies reporting on seasonal influence suggest that childhood UTI is more common in the summer

3.4.6 Prevalence

Prevalence studies have assessed the presence of bacteriuria (predominantly asymptomatic) in the population as UTI itself is a transient and acute illness. Cohorts of children found to have asymptomatic bacteriuria during screening will be made up of those with no discernible history of UTI, some with a

previous history of UTI, and some who have had UTIs but haven't been diagnosed. Thus they constitute a heterogeneous group that will bear some of the characteristics of cohorts of children with previous infection. For the purpose of this guideline, asymptomatic bacteriuria is not regarded as UTI (See Chapter 3.2).

Studies below were population-based and had large sample sizes. Each study was unique, but where they overlapped we observed similarities in findings

A study of school children aged 4-12 in England and Wales found that 1.7% of girls have asymptomatic bacteriuria.[45] A further study in England of school children aged 4-18 found the rate to be higher in ages 7-11 than in age ranges either side. The overall prevalence was 1.9% for girls and 0.2% for boys.[46] A study in Scotland comes to similar conclusions.[47]

A study in Sweden looked at asymptomatic bacteriuria in infancy. The rates for boys were highest in the first two months of life (1.6%), reducing to 0.2% for the cohort aged 8 to14 months (the same rate as studies of schoolchildren). The rates in girls showed an opposite trend rising respectively from 0.2% to 0.5%.[48]

Discussion

The prevalence of asymptomatic bacteriuria shows the same sex differences as symptomatic UTI. It is difficult to say whether the age related patterns differ from symptomatic UTI, as no reliable data exists for overall rates of infection (first-time + recurrent).

Asymptomatic bacteriuria is commonest in boys in early infancy (1.6% under two months) and shows a steady drop thereafter. It affects 0.2% (1/500) of school age boys.

Girls have lower rates than boys until sometime between 8 and 14 months. Between 1.5% and 2% (up to 1/50) of primary school aged girls have asymptomatic bacteriuria. The peak prevalence appears to be in the junior school years (aged 7-11).

The differences in peaks of prevalence rates do not mirror those for first-time UTI. However, recurrent UTI is common and much commoner for girls, reducing only after primary school age (see chapter 5.5). If this is taken into account, the rates of asymptomatic bacteriuria may actually closely related to those of symptomatic UTI.

3.4.7 Recurrence

Many studies identified were case-series of children presenting to Secondary Care settings with recurrent UTI. One study was of neonates alone. Many also had short follow-up times. An Australian reported 46 recurrent UTIs in 34/290 children during 12 months of follow up; 20 children had 1 recurrence; 14 had two or more recurrences.

A study from Sweden showed that 32% of girls and 23% of boys under 10 had a recurrence of UTI, though two or more recurrences were much commoner in girls (8% v 1%).[37] A small study in the USA also found that girls were more prone to multiple recurrences.[49]

An older study from Sweden reported a recurrence rate of 26% in neonates of both sexes; boys under 1 had a recurrence rate of 18%, and boys over 1 had

a recurrence rate of 32%. In girls older than 28 days, the recurrence rate was 40%.[16]

In one UK case-series 41% of children under 1 had a history of recurrent UTI, rising to 73% aged 5 and over. In girls, but not boys, those presenting with recurrent UTI rose with age.[50] A previous study from the same centre suggested that children with scarring developed more recurrences though children with VUR had no increased risk of recurrence.[51]

In another UK study, 78% girls and 71% boys presenting before age 1 had further infections, whereas 45% and 39% respectively had further infections if they presented after the age of 1.[52;53]

Discussion

It is difficult to be sure about rates of recurrence in children in the UK..

Girls are more prone to recurrence and those with recurrent UTI have more episodes than boys. Children who present early in life with UTI are more prone to recurrences. 3/4 children presenting before the age of 1 will have a recurrence. After the age of 1 roughly 40% of girls and 30% of boys will have a recurrence. Girls, but not boys, have increasing rates of recurrence with age. These findings appear to mirror the reported age-specific prevalence data on asymptomatic bacteriuria.

3.4.8 Vesicoureteric Reflux

The reported incidence of VUR ranges from 8-40%, though the majority, including those with the largest samples, showed rates between 20-38%.

The reported rates are very similar in girls and boys. Reflux in girls ranged from 17% to 34% and in boys from 18% to 45%.

The incidence of VUR in the general population was calculated around 50 years ago The calculated population incidence of 1-3% seems reliable. A recent population screening study in Taiwan using ultrasound and assessed the population rate to be 1.26% with four times as many boys affected than girls.[54] Studies suggesting higher rates in girls matched those suggesting higher rates in boys, though the largest studies tended to show that VUR is more common in girls.

A population based study from Sweden (rate of investigation = 97%) showed that under the age of 2, 30% children had VUR - 36% of girls and 24% of boys. 1/3 girls (13% of girls with UTI) had dilated reflux, whereas 2/3 boys had this degree of severity (16%). In this study boys presented earlier than girls.[55]

An earlier study in Sweden reported rates of 34% in girls and 33% in boys. 11% of boys and 8% of girls had dilated reflux.[37] This study also found that in girls reflux was commonest between the ages of 1 and 3

Unilateral and Bilateral VUR

Three studies separately report the numbers of children in their studies with VUR and the numbers of kidneys affected:

31% and 24% respectively in a study from a surgical clinic in Scotland[56]; 29% and 21% respectively in a study from Taiwan[54] ie 55% bilateral [56]; 46%[54]. In a

cohort of girls screened for asymptomatic bacteriuria, 28/82 (34%) had bilateral VUR.[45]

Influence on serious presentations

Higher rates of bacteraemic illnesses are found in children with more severe grades of reflux (III-V): 30% v 16% of matched non-bacteraemic patients.[42]

Fever was a major symptom in more children with VUR.[51] Children managed surgically had less febrile UTIs than those managed medically.[57]

Spontaneous resolution

VUR appears to be worst in the youngest children and to resolve spontaneously in many, however many studies lack the detail to provide more accurate data. Children managed medically may also have had milder degrees of reflux than those managed surgically in non-randomised studies

A large population study from Sweden reports that more severe degrees of reflux occurred in younger children[55] An Italian study produced a similar progression.[40]

A number of studies following up children in outpatient clinics observed spontaneous resolution of VUR. In one study 31%-84% VUR resolved and in two studies improvement without full resolution was noted in a further 15-21%. Dysfunctional elimination syndromes (DES) appear to slow down the resolution of VUR.[58]

A randomised trial of surgical and medical treatment of Grade III-IV reflux found that of those managed medically, 73% had had a reduction to Grade II or less after ten years. Absence of VUR was noted in 47%, and was more likely if they had Grade III VUR at study entry.[59]

In an RCT of antibiotic prophylaxis from the USA.[60] spontaneous resolution of VUR occurred in: 37.5% (grade I), 12.5% (grade II) and 10.3% (grade III).

Recurrent UTIs

A cohort study from Australia found that VUR was present in 14/34 (41%) with recurrent infection and 65/256 (27%) without recurrent infection. Comparison between groups showed that the presence of reflux was not associated with recurrent infection but with the grade of reflux. Bilateral reflux and intrarenal reflux were significantly associated with recurrence. Higher grades of reflux (grades 3 to 5) was the only independent predictor of recurrence (OR 3.6, 95%CI 1.5 to 8.3, $p<0.001$).[61]

Inheritance

The inheritance of VUR may be important in preventing UTI in high-risk newborns.

An evidence-based review reported that from the average of 11 studies analysed, 32% of siblings of affected children also had VUR. Only 2% had reflux greater than grade III.[62]

In an Australian study of infants of mothers with known reflux nephropathy VUR was found in 17/40 (43%).[63]

This supports the laboratory findings of geneticists who suggest a mode of inheritance of autosomal dominance with variable penetrance and expressivity. Exact chromosomal deficiencies have proved elusive[64]

Racial differences in a study in the USA also support this concept: 10% of Afro-Americans investigated had VUR compared to an index rate of 31%.[65]

Discussion

Around 1/3 children with UTI have vesico-ureteric reflux (VUR). VUR is bilateral in around half of cases. The incidence in the general population is probably around 1-3% with equal rates in girls and boys. VUR spontaneously resolves in the majority of children. Girls who present later with UTI may be at increased risk of VUR as a recent study of healthy neonates suggests a much higher incidence of VUR in boys.

One study suggests that severe VUR is more common in infants with bacteraemia than those without bacteraemia. No other studies report on the differential rates of VUR in children presenting with more serious illness.

Severe VUR is likely to contribute to more severe presentations of UTI. VUR is likely to be an inherited condition, and the risk of VUR of siblings equates to that in unselected populations of children with UTI rather than that of the general population.

3.4.9 Structural renal tract abnormality

The most common abnormality in children with UTI is VUR. This is discussed in the section above.

Other common abnormalities included hydronephrosis, obstruction and duplex kidneys. Two larger case-series from the UK suggested duplex kidneys occur in 6-7% of children with UTI, and hydronephrosis in 2.5-7.5% The percentages occurring in normal or other populations of children were not stated.[51;56] In the latter study,13% of children with no VUR had other radiological abnormalities (and a further 4% had minor urethral irregularities). A similar proportion of those with VUR had abnormalities.

A study in Sweden reported that 70% of children with obstruction of the urinary flow presented with UTI in the first two months of life. It is commoner in boys: 10.3% v 2.1% girls. However, girls had more duplex systems: 12% v 5%.[66]

Of 905 neonates in Australia who were investigated for possible sepsis, 64 were found to have a UTI, of whom 12 (19%) had significant non-VUR urinary tract abnormalities.[67]

In China a study using Ultrasound screened 130,000 normal children aged 6 to 15 of whom 1/500 had hydronephrosis.[68]

Severity of presentation

Urinary obstruction is associated with higher rates of bacteraemic illness (9% bacteraemic v 1% of a matched group of non-bacteraemic children).[42]

In another study, 14% of children presenting with pyelonephritis had urinary tract abnormalities compared with 3% who had lower UTI or asymptomatic bacteriuria.[69]

Discussion

Excluding reflux, the most common abnormalities found are hydronephrosis, urinary obstruction, and duplex kidneys. Studies vary quite substantially in their context and findings, and no relevant studies have been undertaken.

Children with urinary obstruction are more likely to present with severe illness, and most will present in infancy.

3.4.10 Other Associations

67% of girls with dysfunctional elimination syndromes (DES) develop UTIs, and of these 20% have VUR. [70] In a study of DES and VUR, half had constipation; and half had either bladder instability or infrequent voiding. A fourth cause of DES, Hinman's syndrome was excluded from the study. DES was associated with an increase in time to resolution of VUR.

The greatest risk of breakthrough infection was from Infrequent voiding, though numerically, constipation was the commonest cause.[58]

Discussion

Dysfunctional elimination syndromes appear to be a risk factor for UTI, and may contribute to slower resolution of VUR. Constipation is the most common cause, but infrequent voiding (<4 times a day) contributes most to breakthrough infections.

3.4.11 Scarring

Rate of scarring

One population-based study in the UK reported that 4.7% of girls and 4.3% of boys presenting with their first UTI had renal scars on DMSA. Logistic regression showed no independent association of scarring with age or sex. The scarring rate remained constant throughout the four years of the study, and the cumulative rate of UTI was 11.3% and 3.6% respectively.[34] From this study 0.53% of all girls in a population will develop scarring, and 0.16% of boys.

A population-based study in Sweden found the annual incidence of scars in girls and boys with UTI to be 9.3/100,000 with a ratio of 2:1.From this study 0.18% of girls and 0.11% boys in a population would be expected to have scarred kidneys.[71]

An early Swedish study suggested that 4.5% girls and 13% boys have scarring.[16] The cumulative incidence of UTI in this study was 3% and 1.1% respectively, giving a population rate of scarring of 0.14%.

A systematic review[72] drew on four prospective studies: 5-15% of children in these studies had evidence of renal scarring.

Another study, which appeared to be population based, gave rates of scarring of 6.4%.[73]

Two studies considered whether scars predated the first suspected UTI: one suggested that 32% to 77% pre-dated the first UTI[69]; the other found that 86% of boys had primary scarring, and only 30% of girls[74] A summary statement on four studies reported that up to 30% of children with VUR had evidence of renal damage in utero.[75] 14% of neonates were adjudged to have congenital dyplasia in one study.[76]

Risk factors

By inference acute pyelonephritis is a cause of scarring. Two studies attempted to confirm this: one found a history of acute pyelonephritis in all children with scarring[69], another was unable to find such a history in 8.8%.[37]

In another study, between half and three quarters of infants and a third of children over 4 were febrile, had vomiting, anorexia, or malaise; and required hospital admission. None of these indicators nor a history suggesting previous urinary tract infections were of value for predicting scarring.[34]

An international study of children with febrile UTI assessed a number of possible risk factors by comparing acute and late DMSA scans. They found late positive scans in:

- 73% of those with recurrent UTI v 56% with first-time UTI;
- 72% with VUR (61% if mild/ 77% if severe) v 52% without;
- 86% the infective organism was non-E Coli v 57% E Coli

In the presence of VUR scarring was more frequent in boys and children older than one year. In the absence of VUR, the only significant factor was recurrent UTI.

Recurrent UTI was a significant factor for girls but not boys[77] however, as recurrence is rare in boys, this may have influenced results.

A large case-series in the UK reported that VUR was associated with scarring in only 19% of cases, unless complicated by recurrent UTI where the rate rose to 46%.[51]

Scarring and reflux

A study in Scotland suggested that reflux was the single most important factor in identifying girls less than one year of age at risk of developing progressive renal damage.[52;53]

A systematic review, however, reported that reflux was only a weak indicator (twice as likely) of the risk of scarring in patients admitted to hospital.[78] A further study in a young age group with a lower incidence of scarring came to similar conclusions. It showed the presence of VUR to increase the chances of scarring from 4% to 16%.[79] Another study compared acute and late DMSA scans: those with severe lesions in the acute scan had an 88% chance of scarring on a late scan; all others with positive scans had a 14-38% chance of scarring; those with normal acute scans had a 0% chance of late scarring.[80]

Scarring and grade of reflux

Most studies indicate an association between scarring and grade of reflux. Most studies reporting on this used the old three-level grading: 5-29% of children with mild Reflux had scars; 28-50% with moderate reflux; 42-100% with severe reflux.[37;45;81-83]

Scarring and other Urinary Tract abnormalities

Children with duplex systems account for 1/3 of those with scarring, and just under a third of children with duplex actually scarred.[82]

Obstructive anomalies accounted for 0-4% of scarring.[72]

Effect of delay in treatment on degree of scarring

One study using a case-control design found differences in severity of scars between children with VUR and delays in treatment: OR 14.1 (95% CI: 1.6-120.9) for any significant delay against no significant delay and OR 2.8 (95% CI: 0.8-9.2) for delay >6 months versus lesser delays.

Do children without reflux get scarring?

A case-series study in Sweden (children< 10 with a definite history of UTI) reported scarring in 5% of those without demonstrable reflux.[37] One study reported that children with negative MCUGs were more likely to develop scarring than those with false negative isotope scans.[52;53]

Recurrent UTI

A cohort study from Australia found that recurrent UTI and recurrent febrile UTI were significantly associated with DMSA abnormalities at one year follow-up.[61]

In one case-series 55% of children over the age of five with a history of recurrent UTI had abnormal scans compared to 15% without such a history.[50] A further case-series found that of children who had experienced one episode of pyelonephritis, 9% had scarring. In children with a history of more than 4 episodes, 58% had scarring.[37]

Scarring and inheritance

Siblings of children with reflux have higher rates of reflux, and more so if they are twins. Reflux is present in 1/3 of siblings, and 1/10 of those have accompanying scarring. Only half have a known history of UTI.[62]

Progressive scarring

One study in the UK followed up group of children diagnosed when aged 3 and 4 for 2-11 years. 1.4% children aged three at presentation had formed new scars. No children aged 4 developed new scars.[84]

A randomised trial of medical or surgical management followed up children with Grades III or IV reflux for 10 years. 14% of children developed new scars in the first five years, but only 1% in 5-10 years. Progressive scarring occurred mostly in children under the age of five and in those with Grade IV Reflux.[85]

A study from Sweden reported 36% of children being followed up intensively had scarring at initial urography. At the final urography after puberty or later, 48% had scarring. The median age of detection was 9.9 years. Over half of those with scarring at final urography had suffered new scars or deterioration.[86]

Another study found that 91% of children developing new or progressive scarring had VUR, especially more severe reflux.[21]

Discussion

Around 5% of children presenting with first-time UTI will have renal scarring. The rate is likely to be similar for boys and girls. The prevalence of reflux nephropathy in the community is greater in girls than boys as UTI is commoner in girls. Rates calculated from 3 studies show that 1/200-1/750 girls in a community will develop Reflux Nephropathy in childhood, and 1/600-1/900 boys. The disparity in rates may reflect differences in imaging techniques and interpretation.

Boys, may be much more susceptible to developing dysplasia or scarring in utero, whereas girls tend to acquire their scarring at a later age, and have a higher correlation with UTI episodes. Almost always, a history of acute pyelonephritis was recorded prior to the discovery of scarring, though not every child who has episodes of pyelonephritis develops scars. The effect of scarring in utero is poorly quantified.

Scarring is much more common in children with VUR, and almost universal in the most severe grades.

The association of VUR and febrile UTI suggests that reflux is both a cause of pyelonephritis and a compounder of its effects.

The situation on new and progressive scarring is not clear.

3.4.12 Long term complications

Hypertension

The incidence of hypertension in the general paediatric population is less than 2%. 8/9 studies included in a 1990 critical review reported rates of 0-13% in children with a diagnosis of VUR and followed up for 18 months to 19 years. One small study of infants with gross VUR and followed up for a prolonged period of time (12-30 years) had much higher rates of hypertension of 38%.[87]

A systematic review collated the prevalence of hypertension following the development of reflux nephropathy. Of the under-20s 5.6%-27.9% and 5.6%-24.7% of the over-20s had hypertension. 3/4 studies reported no difference in risk between those with and those without scarring.[88]

A small but good quality retrospective cohort study showed no difference in mean 24hr blood pressure in patients followed up for 16–26 years after a first UTI. Sub group analysis for markers of severity did not alter results.[89]

A second retrospective cohort study suggested that only those with severe scarring had an increased risk of hypertension over and above normal background risk.[90]

Another study found that the only predictor of hypertension was a positive family history.[91]

Two further cohort studies showed the relationship of hypertension to scarring. The first showed that hypertension only occurred in children with scarred kidneys, or other renal problems.[51] The second in children with UTI and VUR found that hypertension in children and adults was found almost exclusively in those who had scarred.[92] There was one death in the latter group, from the consequences of uncontrolled hypertension.

A longitudinal study with matched controls showed that hypertension was associated with severe scarring[93]

In another longitudinal study in Japan, the development of diastolic hypertension and albuminuria appeared to preface the development of ESRD.[94] In contrast, another study suggested that albuminuria did not predict the degree of renal scarring.[90]

Other studies suggest that the risk of hypertension is large in the general population, and there is no significant increased risk with a history of UTI

A USA study based in a regional centre (managing advanced renal disease) found that only 4% of children being treated for hypertension had a diagnosis of reflux nephropathy. None had severe reflux. Children under 15 had

predominantly renal hypertension, but older adolescents were more likely to have essential hypertension.[95]

Discussion

Hypertension may be associated with UTI in childhood, but the risk is likely to be small and associated only with more severe levels of scarring and/or renal damage. In late adolescence and adulthood, the predominant cause, in those with a history of childhood UTI, appears to be essential hypertension. Most long-term studies are dominated by the presence of essential hypertension, even in at risk groups.

Pregnancy

Two retrospective cohort studies, one in the UK and one in Sweden have evaluated pregnancy complications. The Swedish study noted that bacteriuria was significantly increased in women with a history of childhood UTI. Hypertension was increased in women with severe scarring, but scarring conferred no extra risk if mild or moderate.[96] The UK study used a cohort of women screened for asymptomatic bacteriuria, and subdivided them into groups with complications. Bacteriuria in pregnancy was more common than in controls. Hypertension and pre-eclampsia were both more common in women who had been found to have VUR and scarring (RR 1.3, 95%CI 0.9 to 2.0) compared to controls (RR 3.5 95%CI 0.7 to 16.6).[45]

In a longitudinal study in Australia of women with reflux nephropathy, pre-eclampsia was increased in women with pre-existing hypertension (42%) compared with normotensive women (14%).[63]

Women with mild or moderate renal impairment were at increased risk of renal function deterioration.

Discussion

Few women with a history of childhood UTI have been studied during pregnancy and recruiting sufficiently large samples of high-risk women is fraught with difficulty.

The limited evidence suggests that bacteriuria is more likely; scarring, especially more severe scarring, may be associated with an increase in hypertension and pre-eclampsia during pregnancy. We have not assessed some outcomes such as operative delivery that are likely to be affected by confounding and biases.

Renal insufficiency and failure

The risk of ESRD from chronic pyelonephritis/ reflux nephropathy is published by different renal registries. England and Wales have a rate of 7.3% for 2003; Australia and Sweden both have rates of 4%. Some European countries give figures of over 15%, whereas the USA suggests 0.5%. These discrepancies are likely to reflect different diagnostic practices more than differences in epidemiology. The Australia and New Zealand register includes the diagnostic category of renal dysplasia separately, suggesting that a figure of 4% or slightly less may be a reasonable marker for ESRD due to Reflux Nephropathy

In one study all 20 patients with scarring but no surgical intervention or ESRD followed for 27 years had significantly lower glomerular filtration rate (GFR), and higher diastolic blood pressure and other markers of kidney function than 13 healthy age-matched controls. There was no correlation between recurrent UTI and renal damage, but children with extensive renal damage had the highest rate of ESRD by age 30-40.[93]

The mean GFR in girls having their first episode of proven pyelonephritis before the age of three years was lower than controls. Girls with a later onset of pyelonephritis were no different than controls.[97]

GFR was well preserved in patients followed up for 16 to 26 years except for the seven patients with bilateral scarring.[89]

In Italy, a register of children with chronic renal failure exists as well as that for ESRD. Boys have more severe reflux in association with CRF, and it is usually bilateral. VUR is the principle cause of CRF in children even though it isn't the commonest cause of ESRD.[98]

Another study suggests that boys and girls have equal rates of ESRD caused by UTI.[99]

No child was registered in Sweden as having ESRD as a result of pyelonephritis/ reflux nephropathy between 1986 and 1994.[100] However, in Australia and New Zealand, countries with high vigilance and equally low rates of ESRD attributable to UTI, no improvement in rates had occurred between 1971 and 1998 after changes in diagnostic practice were accounted for. [101]

A study in the USA found that only 5% of children managed in a Regional Centre for advanced disease had a diagnosis of reflux nephropathy, though 9% with ESRD had this diagnosis. All of these had VUR Grade III or worse and bilateral disease.[95]

Congenital dysplasia is suggested as a major cause of ESRD and a study of kidneys removed operatively in children showed dysplasia in 63% of boys and no girls. Four times more boys had surgery than girls and at younger ages.[102]

Discussion

Childhood UTI appears to be associated with a small increased risk of End-Stage Renal Disease (ESRD) in childhood or early adulthood. Chronic Renal Failure (CRF)/ Insufficiency without ESRD, however, may be a much more common outcome.

Some studies suggest that congenital dysplasia, especially in boys causes significant renal morbidity. One national register of CRF has a predominance of boys, but statistics on ESRD do not show the same differences. It is unclear, whether dysplasia causes less morbidity than severe acquired changes related to VUR (particularly bilateral) and scarring.

The conclusions on ESRD rely on the findings of small studies, but since this outcome is otherwise very rare at a young age, it is likely that they are true reflections of the disease process in a small minority of children.

Compensatory growth of healthy kidneys

A study from Sweden identified a group of children who had unilateral scarring. Though the scarred kidneys were smaller at 5-10 years, there was evidence of compensatory growth in the healthy kidneys, and it was estimated that after 15 years the mean renal area would be 98% of normal.[73]

Glomerular filtration rate was found to correlate with renal area in another study[90] but no significant differences were found between women with scarring from childhood UTI and those without.

Overall Discussion

There are no appropriate studies that accurately estimate the risks of long-term complications as a result of childhood UTI. There are problems in linking eventual outcomes to a disease process occurring many years before. The proportion of children (probably restricted to boys) that suffer from congenital dysplasia associated with VUR is difficult to determine, though it may be that many boys who progress to ESRD have this problem.

Clinically significant adverse outcomes probably only occur in a few cases, predominantly in those with severe scarring. When investigating long-term complications, smaller studies do not produce significant results, and any impact of renal disease in large population based studies can be masked by common diseases for example, essential hypertension.

Research recommendation

A well-designed cohort study investigating long-term outcomes including renal scarring and renal function of children with urinary tract infection should be conducted in the UK.

3.5 Risk

It has long been assumed that the risk of a first time childhood UTI progressing to long term kidney damage is significant. In investigating the relationship between UTI and long term damage, we are primarily concerned with ESRD, as the relationship between UTI and other potential morbidities is ambiguous and in most cases, not measurable. Whether kidney damage results from VUR alone or in combination with UTI remains uncertain.

One study estimated that between 10,000 and 15,000 girls would need to be investigated to prevent a single case of ESRD.[103] This level of risk was much lower than previously believed by many. In considering the evidence for risk for this guideline, it was found that the estimate of risk stated above was seriously flawed. Annual incidence of ESRD in the population was used to arrive at the estimate, rather than cumulative incidence, resulting in a significant underestimate of risk based on the assumptions used in this study. Further evidence examining the link between childhood UTI and ESRD was sought.

It was found that evidence from renal registries and published estimates showed that the true risk of ESRD developing as a result of UTI in childhood is highly uncertain; information from registries is often not specific about the cause of ESRD. UTI in childhood often goes undiagnosed (See appendix A), making it difficult to arrive at an accurate estimate of the true risk.

Given the degree of uncertainty around the key assumptions and data used by the study considered above, and discussions within the GDG, no reliable estimate of the risk of UTI leading to ESRD can be calculated. It is not clear what the true rate of ESRD caused by CP/RN is, nor is it clear what proportion of these cases have had a UTI in childhood. Without reliable estimates of these figures, as well as of lifetime risk, the level of uncertainty in the model in Appendix A is such that no reliable conclusions can be drawn based on the published data alone.

4 Diagnosis

4.1 Introduction

Most children in the United Kingdom would present to primary care or an emergency department with a first time UTI.

The clinical presentation may be influenced by several factors including the age of the child, the anatomical location of the infection in the urinary tract, the extent of verbalisation in the child or even by the stage in their toilet training.

Urinary tract infection in children presents in a variety of ways. It is a differential diagnosis with a spectrum ranging from a septic neonate to a teenager with frequency and dysuria.

Several predisposing factors have been alluded to historically. These include water intake, level of cleanliness and personal hygiene, dietary and other social factors.

UTI is predominantly a clinical diagnosis and is based on index of suspicion in the appropriate clinical context and aided by the use and availability of different diagnostic tools.

The appropriateness of an accurate diagnosis depends on the clinical situation

The aim of diagnosis is to aid prompt symptomatic management, direct appropriate investigations and reduce both short and long term morbidity and mortality associated with the condition its management.

Once a clinical suspicion of UTI has been raised, it becomes important to obtain a urine sample to direct further management. This may not be required in a patient with a clinically obvious first time lower tract UTI.

In this section we have explored the evidence base behind the predisposing factors and attempted to create a clinical management model for first time UTI.

The cost implications range from that associated with treatment, the use of different diagnostic modalities to direct future care and the morbidities stemming from the condition and its management.

There is considerable variation in this practice and therefore there is a need for robust guidance, based on available evidence of the highest level. This has been coupled with good practice statements in areas where there are shortfalls in published knowledge.

4.2 Predisposing factors

Sixteen studies were identified which investigated the predisposing factors for a first-time UTI in children.

4.2.1 Host susceptibility factors

Age, gender, race, underlying concomitant disease.

Eight studies were identified investigating host susceptibility factors in children.[37;104-110] All studies reported age and gender differences, however only one study reported race.[105] One study investigated phimosis.[110]

A case-series study from the United States investigated 100 children aged 5 days to 8 months (mean 2.1 months) who were hospitalised for first known

UTI.[104] Male infants accounted for 75% of UTI cases within the first three months of life compared with 11% of infants who were 3 to 8 months of age. Of the 41 infants who were under 30 days old, 33 (81%) were boys.[EL 3]

A cross-sectional American study investigated distribution of asymptomatic bacteriuria in 3057 school-aged children.[105] No boys were found to have bacteriuria and 12/1267 girls between the ages of 6 to 15 had first time UTI. 8/772 (1.0%) girls between age 6 to 10 years; 4/495 girls (0.8%) for 11 to 15 age group. One school with black children only participated in the study. Again, no boys were found to have bacteriuria and 0.9% of 115 girls had UTI.[EL 3]

A case-series study from Turkey retrospectively investigated 71 neonates aged 18.1 days (±11.2 days) in whom UTI was diagnosed during the first 4 weeks of life.[106] There were 54/71 (76.1%) boys and 17/71 (23.9%) girls with UTI, of which 40.8% (29/71) were preterm (gestational age range between 27 and 37 weeks).[EL 3]

A case-series study conducted in Sweden investigated 1177 children aged 10 or younger with their first symptomatic UTI.[37] In boys 133/225 (59%) cases were detected before the age of one and in girls, 181/952 (19%) of UTIs were detected before the age of one.[EL 3]

A cross-sectional study conducted in the USA identified clinical and demographic factors associated with UTI in febrile infants who presented to an emergency department and were ≤60 days old.[107]

Being uncircumcised (OR 11.6 (95%CI 5.0 to 26.6))and having temperature >39°C (OR 2.5 95%CI (1.6 to 4.0)) were associated with an increased risk of UTI. In multivariable analysis, being uncircumcised (p<0.001) and height of fever (p<0.001) remained associated with UTI (EL3)

	Factor present	Factor absent	Bias-corrected 95%CI
Uncircumcised (vs. circumcised male)	62/291	6/262	11.6 (5.0 to 26.6)
Max temperature >39°C (vs. <39)	34/209	57/796	2.5 (1.6 to 4.0)
Female (vs. circumcised male)	22/439	6/262	2.2 (0.9 to 5.5)
Age <28 days (vs>28 days)	37/334	54/671	1.4 (0.9 t 2.2)
Ill appearing (YOS>10)	4/71	87/924	0.6 (0.2 to 1.6)

A study conducted in Sao Paulo analysed the contribution of risk factors to the occurrence of urinary tract infection in 61 full term newborn infants (26 boys, 35 girls) presenting with a positive bag culture and fever (>37.8ºC), weight loss (>10% of birth weight) or non-specific symptoms (feeding intolerance, failure to thrive, hypoactivity, irritability).[108] On presentation, another urine sample was collected by SPA to confirm diagnosis and 42 infants were found to be culture negative (group I) and a diagnosis of UTI was confirmed in 19 (group II). There were no significant differences between groups for birth weight, sex, asphyxia or membrane rupture time. On presentation there were no differences between the groups for fever (p=0.31), however there were significant differences for weight loss (>10% of birth weight) (p=0.01) and non-specific symptoms (p=0.0004)

Children who had urinary tract infection confirmed by SPA were significantly more likely to have associated infectious diseases (RR 3.27 (95%CI 1.15 to 7.04, p=0.0001); be using broad spectrum antibiotics (RR 3.03 (95%CI 1.51 to 6.08) p=0.012); have renal and urinary tract malformations (RR 2.97 (95%CI 1.57 to 5.64) p=0.007); be on mechanical ventilation (RR 2.99 (95%CI 1.61 to 5.53) p=0.029); be on parenteral nutrition (RR 5.05 (95%CI 2.72 to 9.39) p=0.0009); and have an intravascular catheter (RR 3.27 (95%CI 1.84 to 5.83) p=0.009).[EL 3]

A case-series study conducted in the Philippines evaluated whether unexplained and/or excessive jaundice was associated with UTI in 54 jaundiced infants (22 boys, 32 girls) aged less than 8 weeks of age.[109] Of the 54 included infants, 5 had UTI and 49 did not. There were no significant differences in demographic or historical characteristics between groups in terms of gender, age, place of birth, mode of delivery, birth weight, gestational age, neonatal infection, or onset of jaundice. Similarly, there were no significant differences in maternal characteristics between groups in terms of maternal age, gravidity, presence of maternal infection or maternal illness. There were significant differences in total, direct and indirect bilirubin levels between infants who had and did not have UTI.[EL 3]

Phimosis

One Japanese case-control study found that boys younger than 7 months with foreskins that could not be retracted to expose the external meatus were at 7.8 times higher risk for febrile UTI when compared with boys with foreskins that could be retracted to expose the external meatus (95% CI 3.99 to 15.31).[110] This study, however, suffers from a fundamental flaw due to the fact that phimosis is physiological at this age and should be interpreted with caution. Additionally, not all the results from the analysis were reported making it difficult to assess quality. [EL 2-]

No studies on blood group as a predisposing factor for UTI in children were identified.

4.2.2 Familial renal disease

VUR incidence is covered in the introduction within the Epidemiology section and is also included in the section on recurrence. The following two studies were identified, which only investigate the likelihood of VUR in siblings of children with VUR, the majority of whom did not have a history of UTI.[111;112].

Using an awake voiding cystogram, an American case-series study assessed 104 siblings aged 3 months to 15 years of patients with VUR (irrespective of history of UTI).[111] Of the siblings, 34 (32.7%) were found to have VUR and among those with VUR, 6 (17.6%) had a history of UTI and 25 (73.5%) had no history of UTI. The remaining 3 were reported to have abnormal voiding patterns but their UTI history was not reported.[EL 3]

A case-series study conducted in Iran investigated the number of VUR cases in 40 children with siblings diagnosed with VUR.[112] 17 (43%) siblings of 34 patients with VUR (irrespective of history of UTI) had VUR. Of the 17 with VUR, 5 (29.4%) also had a history of symptomatic UTI. VUR was bilateral in 6/17 and unilateral in 11/17 of the siblings.[EL 3]

No studies on kidney stones or genetics as predisposing factors for UTI in children were located.

4.2.3 Religious and cultural practices

Circumcision

Seven studies have investigated the association between circumcision and risk of UTI.[113-120]

An Australian meta-analysis looked at the effect of circumcision on the risk of UTI in boys in twelve studies. The meta-analysis included one RCT, four cohort studies and seven case-control studies.[113]

The RCT was a study of recurrent UTI in 70 uncircumcised boys with proven UTI aged 3 months to 10 years who were randomised to circumcision or no circumcision and showed an OR of 0.13 (95%CI 0.01 to 2.63).

Four cohort studies were conducted in hospital settings in boys aged 1 to 3 years and showed benefit with a summary OR of 0.13 (95%CI 0.07 to 0.23), however there was significant heterogeneity between these studies (x^2 = 82.48, df = 3, p<0.001). When one outlying study was excluded, the heterogeneity was not significant (p=0.64)

The seven case-control studies were conducted in secondary care settings. Six of the seven studies were in boys aged 1 month to 5 years in hospital care settings, and one study was in adults attending a community sexually transmitted disease clinic. The case-control studies included showed benefit with a combined OR of 0.13 (95%CI 0.07 to 0.23). There was no significant heterogeneity between these studies (x^2 = 8.15, df = 6, p = 0.2)

The summary OR across all study types was 0.13 (95%CI 0.08 to 0.20). There was no significant heterogeneity observed between study types (x^2 = 0.16, df = 2, p = 0.9), however significant heterogeneity was observed within the individual studies (x^2 = 90.63, df = 11, p<0.0001) owing to the inclusion of the cohort studies. Without the cohort studies, there was no significant heterogeneity (x^2 = 10.92, df = 10, p<0.4).

The odds of a circumcised boy having a UTI are about 0.1 when compared with uncircumcised boys. While circumcision may be protective against UTI, the risk-benefit of circumcision is not easily quantifiable. The study concludes that while circumcision substantially reduces the risk of UTI, routine circumcision should not be considered. Circumcision has a potential role in boys with past history of recurrent UTI, or with high grade VUR, as the benefits in these cases may outweigh the risk of complications.[EL 2++]

An American cohort study of 28,812 infants found that the median age at diagnosis of UTI was 2.5 months for uncircumcised males, 4.5 months for circumcised males and 6.5 months for female infants.[114] The incidence of UTI in the first year of life was 1:47 for uncircumcised males, 1:455 for circumcised

males and 1:49 for females. Circumcised males had significantly fewer episodes of first time UTI (OR 9.1, 95%CI 5.2 to 15.7)[114] [EL 2++]

In a retrospective cohort study of all 136,086 boys born in USA army facilities from 1980 to 1985, medical records were examined to determine any association between UTI and circumcision during the first month of life.[115] Significantly more UTIs occurred in the boys who were not circumcised (p,0.001) when compared with boys who were circumcised.[EL 2+]

In an American cohort study of 5261 infants born at an army hospital from 1982 to 1983, 400 (7.6%) infants were evaluated for UTI in the first year of life and forty-one of the infants (0.78%) were subsequently diagnosed with UTI.[116] Among the 41 with UTI, 13 were female, 4 were circumcised males, and 24 were uncircumcised males. The incidence of UTI in males was higher than in females (28/2502 v. 13/2759, p<0.01) and the incidence of UTI in uncircumcised males was higher than in circumcised males (24/583 v. 4/1919, p<0.001).[EL 2+] An evaluation of all infants born in army medical facilities from 1975 to 1984 (n=427698) confirmed these findings.[117] Females were significantly more likely to have UTI in the first year of life when compared with males (0.51% v. 0.28%, chi square = 143.5, p< 0.001) and circumcised males were less likely to have UTI in the first year of life when compared with uncircumcised males (0.09% v. 1.0%, chi square = 1086.4, p<0.001).[EL 2+]

A Canadian cohort study identified 69,100 boys who had been circumcised within the first month of life. The risk of hospitalization for UTI decreased with

age, but remained higher for boys who were uncircumcised.[118] At one month after birth, the probability of hospital admission for UTI (per 1000 person-yrs) was 4.5 times higher for uncircumcised boys when compared with circumcised boys (95% CI 2.4 to 8.4). Subsequent risk at one and three years was 3.7 (95% CI 2.8 to 4.9) and 3.0 (95% CI 2.4 to 3.8), respectively, with 195 circumcisions needed to prevent 1 hospital admission for UTI in first year of life. [EL 2++]

An Australian case-control study recruited boys under 5 years old and compared 144 boys with UTI (median age 5.8 months) with 742 boys without UTI (median age 21.0 months).[119] Of they boys with UTI, 2 (1.4%) were circumcised compared with 47 (6.3%) of the controls (p=0.02). There was no evidence that age was a confounder or modified the protective effect of circumcision.[EL 2+]

An American case-control study compared 36 boys with UTI to 76 controls. Male infants less than 1 year old presenting with first time UTI were significantly more likely to be uncircumcised when compared with male infants without UTI.[120] This was true regardless of age (<3 months and >3months, all p <0.0001), ethnic group (white, Black and Hispanic, all p ≤ 0.02), and socio-economic status (using type of medical insurance as a proxy, all p ≤ 0.02). [EL 2+]

4.2.4 Lifestyle considerations

Breastfeeding

A case-control study conducted in Sweden aimed to investigate the association between breast-feeding and the risk of first time febrile UTI.[121] Cases (n=200) and controls (n=336) were recruited consecutively in two paediatric departments in Sweden and matched for gender and age. Of children aged 0-6 years, presenting for the first time with symptomatic UTI, exclusive breastfeeding was found to have a protective effect on the risk of UTI. The risk of UTI was 2.3 times higher in non-breastfed children when compared with exclusively breastfed children (95% CI 1.56 to 3.39). The protective effect of breastfeeding was dependent on the duration of breastfeeding as well as the gender of the child or infant. A longer duration of breastfeeding was associated with a lower risk of infection after weaning and the effect was stronger in girls (hazard ratio = 3.78) than in boys (hazard ratio = 1.63).[EL 2+]

Use of nappies

A case-control study conducted in Finland compared disposable, superabsorbant and washable cotton nappies on children presenting with their first UTI.[122] No differences were found (disposable OR: 0.95, 95% CI 0.62 to 1.46; superabsorbant OR: 1.04, 95% CI 0.69 to 1.57; washable cotton OR: 1.00, 95% CI 0.46 to 2.16). [EL 2+]

Hygiene

In a case-control study from the Philippines, the association between UTI and urination, defecation, washing and bathing habits was investigated in children aged 6 to 12 years (n=23 cases, n=23 controls).[123] Bathing habits (daily vs. less than daily), urinary frequency (less than 5 times/day or 5+ per day), holding urine during the day (yes or no), permission to urinate at school (during break v. whenever), washing after urination (yes or no), washing after defecation (yes or no), direction of washing (from behind v. from front), and use of soap during washing (yes or no) showed no association with risk of UTI. The study did not specify whether the controls were matched for age and gender, selection criteria were not explicit, withdrawals were not explained and the small sample size resulted in wide confidence intervals. [EL 2-]

Voiding habits

In a Swedish cross-sectional study, 1557 children (aged 6 to 9) and their parents/carers responded to questionnaires (56% response rate) regarding voiding habits.[124] Nearly 10% of girls (75/823) and 3% of boys (20/728) reported a previous history of UTI. Although the numbers of boys with previous UTI was too small to draw any conclusions, symptoms suggesting emptying difficulties were seen significantly more often in girls with previous UTI when compared with girls with no history of UTI, including:

- bed wetting ($p = 0.002$)
- day wetting ($p < 0.0002$)

- does not reach toilet (p=0.03)
- prolonged voiding (p<0.002)
- poor stream (p<0.003)
- staccato voiding (p<0.006)
- able to void again (p<0.002)
- straining (p=0.02)
- manual compression of abdomen (p<0.003)
- encopresis (p=0.03)

The daily frequency of micturition between children who reported a history of UTI was not statistically different from those who did not report a history of UTI.[EL 3]

Evidence summary

First UTI is more common in infancy.

UTI is more common in girls.

The incidence in males is highest before the age of three months.

In females the incidence rises from three months and between the ages of six and eight months is higher than in males.

In infancy the median age for diagnosis of UTI is between 2.5 and 4.5 months in male and 6.5 months in female infants.

The risk of UTI is lower in circumcised boys than in non-circumcised boys (OR 9.1, CI 5.2 – 15.7) ARR 11 (tenfold). One hundred and ninety five infants need to be circumcised to prevent one case of UTI requiring hospital admission.

In addition to other benefits, breastfeeding has a protective effect against UTI and is more pronounced in female infants. This is dependant on the duration of breast feeding and the effect appears to persist even after weaning.

No studies were identified evaluating the association between ethnicity, blood groups, familial susceptibility or renal stones and UTI in children. Similarly no good quality studies were located evaluating the association between phimosis and UTI. No good quality studies were identified to link other personal hygiene, religious or social factors to UTI in children.

The type of nappy was not shown to affect the risk of UTI.

Translation

The reviewed evidence shows that there is a lower incidence of UTI in boys who are circumcised. The evidence for circumcision has not been evaluated by this guideline and the risks and benefits have not been fully considered.

Recommendations

Women should be made aware that breast-feeding, among other benefits, is likely to offer protection against UTI in infants.

Research recommendations

More studies with adequate sample sizes are needed to evaluate the effectiveness of breastfeeding, nappies and hygiene in preventing childhood UTI.

4.3 Symptoms and signs

Fifteen studies were identified reporting signs and symptoms in children presenting with UTI. The majority of studies reported symptoms in children treated for UTI in secondary care[14;16;21;40;42;51;104;125-130] while two studies reported symptoms of children presenting to a GP[36;131]

A case-series study conducted in Australia described the clinical features of 305 children under the age of 5 who presented consecutively at an emergency department with first time symptomatic UTI.[125] The most commonly reported symptoms were fever (80%), an axillary temperature higher than 37.5 (60%) irritability (52%), anorexia (49%), malaise (44%), vomiting (42%) and diarrhoea (21%). Less common symptoms in fewer than 20% of children were dysuria, offensive urine, abdominal pain, frequency and haematuria.[EL 3]

A case-series study from the United States reported signs and symptoms from 100 children aged 5 days to 8 months (mean 2.1 months) who were hospitalised for first known UTI.[104] Fever was the most common symptom (63%) and irritability was reported in over half of the children (55%). Other symptoms included refused feeds (38%), vomiting (36%) and diarrhoea (31%). Less common symptoms were abdominal distention and jaundice were reported in 8% and 7% of the children, respectively.[EL 3]

A case-series study was conducted in the USA in 83 boys aged 2 weeks to 14 years presenting to a children's hospital with first time UTI(25% ≤1 year old and half < 6 years old).[126] Fever was present in 40 (48%) of the children and the only presenting sign in 25%. Other symptoms included overactive bladder syndromes in 23 (28%), abdominal or flank mass in 11 (13%), enuresis in 7 (8%) and gross haematuria in 6 (7%).[EL 3]

An Italian multi-centre cross-sectional study presented symptoms of 227 children admitted to one of nine paediatric departments with first time acute pyelonephritis of whom 218 (96%) presented with fever.[127] Of the children who presented with fever 114 (52%) experienced other symptoms before the onset of fever.[EL 3]

A case-series study of children aged 0 to 14 years (64 children under 12 months) in Italy described 223 children presenting to a hospital with first time UTI.[40] Presenting symptoms included fever in 144 (65%), dysuria and

frequency (41%), gastrointestinal symptoms in (19%), haematuria in (11%), failure to thrive in 14 (6%), and jaundice in 2 (1%).[EL 3]

A case-series study in the UK investigated 120 children (aged 2 weeks to 12 years) who had a UTI and underwent an IVU.[21] Presenting symptoms were fever in 77% (57/74), abdominal or loin pain in 46% (34/74), chronic constipation in 21% (16/74) and uncoordinated voiding with residual urine in 11% (8/74).[EL 3]

An case-series study in Finland presented population surveillance data of children aged one week to 9.5 years (median age 0.125 years) and reported on symptoms of UTI in 134 children with first time bacteremic UTI.[42] The most common presenting symptoms were fever (92%), and irritability (60%). Other symptoms included abnormal crying (34%), vomiting (16%), lethargy (26%), feeding problems (20%), abdominal pain (7%), dysuria (1%) and convulsions (4%). National Surveillance data were used to compare the results with 134 children with first time non-bacteraemic UTI. The only significant difference reported was for feeding problems (20% v. 10%, p = 0.02).[EL 3]

An RCT conducted in Turkey investigating the effectiveness of circumcision on recurrent UTI and described the presenting symptoms of 88 boys referred to a Paediatric Nephrology Department with first time UTI.[128] The most common presenting symptoms were fever <38.5°C (48%), dysuria/frequency (34%) and fever >38.5°C (24%). Other reported symptoms included vomiting

and/or diarrhoea (22%), enuresis (7%), suprapubic discomfort (11%), abdominal pain (18%), flank pain (5%) and offensive urine (2%).[EL 3]

A case-series study conducted in the UK recruited 744 children with UTI, aged 0 to 12 years treated in a hospital.[51] Fever was a presenting symptom in 42%. Other reported symptoms included abdominal or loin pain (31%) and enuresis (38%) which was only identified in children over 5 years. A significantly greater proportion of children with VUR (141/246) presented with fever compared with children without VUR (173/498; 57.3% v. 34.7%, $p<0.001$).[EL 3]

A case-series study from the UK reported symptoms of 14 children with UTI aged 15 years or younger in a semi-rural general practice.[36] 6 children (40%) presented with dysuria and frequency, 3 (20%) with abdominal pain, 2 (13%) with enuresis, and 1 each (7%) with loin pain, haematuria and failure to thrive.[EL 3]

A case-series study conducted in the UK reported the clinical and laboratory features of 49 boys (aged 2-12) presenting to primary care practices with UTI.[131] The most common presenting symptoms were dysuria/frequency (82%), abdominal pain (35%) and enuresis (45%). Other reported symptoms included fever (26%), haematuria (20%) and balanitis (20%). [EL 3]

A study conducted in a GP practice in the UK presented the clinical findings of 38 children (12 boys and 26 girls) aged under 15 with culture proven UTI

(>10^5cfu/ml in a clean catch urine sample).[129] Dysuria was present in 27/38 children (71%) and was the most common symptom. 12 children (32%) presented with abdominal pain; 5 (13%) presented with loin pain/tenderness; 9 (24%) with enuresis; 8 (21%) with fever; 7 (18%) with offensive urine; 2 (5%) with daytime incontinence; 1 (3%) with haematuria and 1 (3%) with rigor.[EL 3]

1 **Table 4.3.1 Summary of presenting symptoms**

2

Study	Craig 1998[125]	Ginsburg 1982[104]	Burbige 1984[126]	Pennesi 1998[127]	Messi 1988[40]	Smellie 1985[21]	Honkinen 2000[42]	Nayir, 2001[128]	Smellie 1981[51]	Dickinson, 1979[36]	Hallett et al, 1976[131]	Brooks 1977[129]
Age	<5 yrs	5d to 8m	2wks to 14yrs	15d to 4 yrs	<14 yrs	2 wks - 12 yrs	1wk - 9.5yrs	3mo - 10yrs	≤12yrs	≤15yrs	2 to 12yrs	<15 years
Study size (n)	305	100	83	227	223	120	134	88	744	14	49‡	38
Setting	Hospital	Hospital	Hospital	Hospital	Hospital	Hospital	Hospital	Hospital	Hospital	Primary care	Primary care	Primary care
Country	Australia	USA	USA	Italy	Italy	UK	Finland	Turkey	UK	UK	UK	UK
Symptom (%)												
Fever	60	63	48	96	65	77	92	72	42	-	26	21
Irritability	52	55	-	-	-	-	60	-	-	-	-	-
Vomiting	42	36	-	-	-	-	16	22**	-	-	-	-
Anorexia	49	-	-	-	-	-	-	*see vomiting*	-	-	-	-
Diarrhoea	21	31	-	-	-	-	-	-	-	-	-	-
Enuresis	-	-	8	-	-	-	-	7	38†	14	45	24
Dysuria	15	-	-	-	41*	-	1	34*	-	43*	82*	71
Frequency	10	-	-	-	*see dysuria*	-	-	*see dysuria*	-	*see dysuria*	*see dysuria*	-
Abdominal pain	13	-	-	-	-	46***	7	18	31	21	35	32
Smelly urine	13	-	-	-	-	-	-	2	-	-	-	18
Haematuria	7	-	7	-	10.8	-	-	-	-	7	20	3
Failure to thrive	-	-	-	-	6.3	-	-	-	-	7	-	-

Malaise	44	-	-	-	-	-	26	-	-	-		-
Poor feeding	-	38	-	-	-	-	20	-	-	-	-	-
Constipation	-	-	-	-	-	21	-	-	-	-	-	-

*reported with frequency

** reported with diarrhoea

*** reported with loin pain

† in children aged 5 or older (n=355)

‡ all male

A Saudi Arabian observational study investigated symptoms of UTI in 1081 children by age group (0 to 1 year, 1 to 2 years, 2 to 5 years, and 5 to 12 years).[130] In the 0 to 1 year old age group (n=221), the most common symptom was vomiting (23%) followed by fever and irritability (11%). This reversed in the 1 to 2 year old group (n=265), with fever and irritability being reported more often than vomiting (38% and 29%, respectively). No other symptoms were reported for these two age groups. In the older age groups (n=248 and n=347, respectively), the most common symptoms were fever and irritability (60% and 48%, respectively) followed by frequency/dysuria in the 2 to 5 year old group (26%) and abdominal pain in the 5 to 12 year old age group (44%).[EL 3]

A case-series study conducted in Sweden described fever (≥38°C) as one of the clinical features of children aged 0 to 16 years presenting at a children's or maternity hospital for symptomatic UTI.[16] The number of children presenting with fever decreased with age. In infants 1 – 12 months 179/186 (96%) presented with fever; in children 1-3 years 70/96 (73%) presented with fever; in children 3-10 years 120/200 (60%) presented with fever; in children 10-16 years 19/41 (46%) presented with fever.[EL 3]

In an American prevalence study, UTI occurred in 50/945 (5.3%) febrile infants less than 1 year old presenting to the emergency department of a children's hospital. UTI was found to occur significantly more often among infants with no identified source of fever (34/454) when compared with infants with a condition

identified as a possible source of fever (15/429; 3.5% v. 7.5%, p = 0.02).[14] UTI was least prevalent among infants with an unequivocal source of fever (1/62).[EL 3]

Evidence summary

Limited evidence shows that the commonest symptoms of UTI in children presenting to primary care are frequency and dysuria.

The commonest symptoms and signs of UTI in children presenting to hospital are fever, irritability, malaise and gastro-intestinal symptoms. Other less common symptoms include dysuria, frequency, abdominal pain, failure to thrive, smelly urine and haematuria. Rarer symptoms include bed wetting, problems with voiding, manual compression of abdomen and encopresis.

UTI is more frequent among infants with no obvious focus of fever compared with those in whom there is an obvious focus.

Translation

The majority of the included studies are of children treated at secondary care centres and does not represent the majority of children who present with a UTI.

Symptoms can broadly be divided into non-specific symptoms and symptoms specifically characteristic of UTI. Non-specific symptoms such as fever, irritability, lethargy and vomiting are more likely to be due to UTI in infants, particularly in those in whom there is no alternative diagnosis.

Although diarrhoea can be associated with UTI it is rarely the main symptom and further, it is often difficult to get a good quality urine sample for testing for UTI in the presence of diarrhoea. There should be a high threshold for urine collection in infants and children when the cause is most likely to be due to acute viral or bacterial gastroenteritis.

Generally, symptoms of UTI were not well reported and consensus was required to generate the following table of symptoms which is intended to indicate symptoms that are most likely to be encountered in a child with UTI. It is not a comprehensive list, and presenting symptoms combined with dipstick urine testing and clinical judgement should be considered when diagnosing UTI.

Recommendations

Neonates with any signs or symptoms (Table 4.3.2) should have a urine sample tested.

Children who are unable to communicate their symptoms and have two or more clinical signs or symptoms (Table 4.3.2) should have a urine sample tested. UTI should also be considered in children with unexplained persistent symptoms or signs.

Children who are able to communicate their symptoms and present with any of most common symptoms or signs or two or more less common symptoms or signs should have a urine sample tested.

Table 4.3.2 Presenting signs and symptoms in children with UTI

Age Groups		Most common → Least common		
Neonates		Fever Vomiting Lethargy Irritability	Poor feeding Failure to thrive	Abdominal pain Jaundice Haematuria Offensive urine
Children	Pre-verbal	Fever	Abdominal pain or abdominal/loin tenderness Vomiting Poor feeding	Lethargy Irritability Haematuria Offensive urine Failure to thrive
	Verbal	Frequency Dysuria	Dysfunctional voiding Changes to continence Abdominal/loin pain or tenderness	Fever Malaise Vomiting Haematuria Offensive urine Cloudy urine

Any child can present with septic shock secondary to UTI, although this is more common in infants.

Fever defined as >38°C

Research recommendations

Combined population based studies in primary and secondary care, with larger sample sizes are needed to evaluate the association between signs and symptoms and UTI.

4.4 Clinical features of UTI

4.4.1 Localising UTI by clinical signs/symptoms

A systematic review identified 10 studies assessing various clinical features for the localisation of UTI in children.[132]

Two studies compared body temperature to the reference standard of DMSA for diagnosing acute pyelonephritis. Test performance was poor in both studies with one reporting sensitivity of 87% and specificity of 40% for cut-off value of 39.1°C and the other reporting sensitivity of 87% and specificity of 64% for cut-off value of 38°C.

Two studies evaluated the diagnostic accuracy of symptoms of acute pyelonephritis using DMSA as the reference standard. Sensitivities of 57% and 71% were found with specificities of 100% in both studies.

One study assessed the presence of physical symptoms or positive laboratory findings for the diagnosis of acute pyelonephritis using DMSA as the reference standard. Sensitivity was 98% and specificity 33%.

Evidence summary

Clinical features used and the methods of determination were diverse and poorly described. They cannot used to predict pyelonephritic changes on DMSA.

4.4.2 Severity of urinary tract infection

Translation

The GDG recognise the importance of defining the severity of illness in children with urinary tract infection. The definition of severe urinary tract infection has been derived from the Fever in Children Guideline (due for publication May 2007) and clinical experience of the GDG. The other definitions are based on the models defined in the Cochrane systematic reviews for antibiotic management of UTIs which have been adopted by the GDG. Despite the poor evidence for using clinical features to localise UTI, it is appreciated that initial management is still dependant on the clinical presentation. The above approach has relied on a model that was utilised in randomised controlled trials to initiate treatment of UTI, based on a clinical suspicion of severity rather than attempting accurate anatomical localisation.

Recommendation

Children with suspected UTI and the following the signs and symptoms should be considered to be *Severely Ill*:

- Signs of dehydration
- Reduced activity/responsiveness
- Pale / mottled / ashen skin or blue
- Ill appearing

Children with suspected UTI, fever > 38^{O} C and at least one of the following features should be considered to be *Systemically Unwell:*

Loin or abdominal pain or tenderness, vomiting, irritability, poor feeding, chills and rigors

All other children with suspected UTI but no systemic features, should be considered to be *Systemically Well*.

4.5 Urine collection

Accurate diagnosis of UTI is essential to avoid inappropriate over or under treatment and investigation. To establish an accurate diagnosis of urinary tract infection requires the collection of an appropriate urine sample. Since the majority of children presenting with a UTI in the United Kingdom are likely to present in primary care, the collection of a urine specimen needs to be simple, reliable, cost effective and acceptable to children, parents and carers.

Instructions to families need to include clear detailed information about the practicalities of the method used and advice about appropriate skin cleansing.

A variety of methods are used in primary care, predominantly 'clean catch', urine collection pads (Euron) or urine collection bags. Other methods sometimes used to collect urine including gauze, cotton wool balls, sanitary towels and panty-liners placed in the nappy and often lead to inaccurate results because of bactericidal agents incorporated in these materials rendering them unsuitable.

In hospitals additional methods are available including supra pubic aspiration (SPA) and samples taken using catheterisation. Whilst being advocated in the literature as the ' reference standard' to collect urine, supra pubic aspiration (SPA) is invasive, unpleasant for the child and is dependent upon skilled practitioners to perform. Specimens collected in this way may be contaminated (by skin or gut flora) in the same way as blood cultures can. It is also not suitable as a method of urine collection in primary care. However in a hospital environment, when a child is acutely unwell and commencement of antibiotics is urgent it may be appropriate to use an invasive method such as SPA or urethral catheterisation.

The costs associated with urine collection include not only the costs of materials used and personnel time collecting and processing the urine, but also the costs

of misdiagnosis. Failure to accurately diagnose a urine infection may result in treatment delay and may increase the likelihood of renal parenchymal defects. All urine collection methods have a contamination rate and may lead to misdiagnosis and unnecessary investigation. Urine collection bags are unpleasant for the child, costly and not environmentally friendly. Pads may be useful if used correctly they are inexpensive and user friendly. The material cost of clean catch specimen is negligible but it may be time consuming, however, some parents/carers have expressed a preference for this method.

A systematic review identified twelve studies, with 16 different test evaluations, comparing the diagnostic accuracy of different methods of urine collection. The review found that only half studies included an appropriate spectrum of patients and provided an adequate description of patient selection. The systematic review also found that possible review bias (blinding) was not reported in any of the studies and that a quarter of studies did not provide an adequate description of the index test or reference standard. [132][EL 2++]

4.5.1 Clean voided urine samples

A systematic review[132][EL 2++] identified five studies (with seven data sets) that assessed the diagnostic accuracy of a clean catch urine sample, with SPA urine sample as the reference standard. All studies were judged to be of reasonable

quality. Half of the studies were in children aged 0 to 12 years and half were in children aged under 3 years with a mean age of around 4 months.

Sensitivity ranged from 75% (specificity 96%) to 100% (specificity 100%) and specificity ranged from 57% (sensitivity 83%) to 100% (sensitivity 100%). The positive likelihood ratios ranged from 1.9 (LR- 0.30) to 47.7 (LR- 0.08). Negative likelihood ratios ranged from 0.08 (LR+ 47.7) to 0.36 (LR+ 3.57). Although there was considerable heterogeneity all studies were clustered towards the top left of the receiver operator characteristic (ROC) curve suggesting that acceptable diagnostic performance is obtained from clean voided urine samples.

There was considerable heterogeneity in pooled positive likelihood ratios ($p<0.0001$) however the negative likelihood ratios were statistically homogeneous ($p=0.504$). The pooled positive likelihood ratio was 7.7 (95%CI 2.5, 23.5) and the pooled negative likelihood ratio was 17.8 (interquartile range 6.6, 19.5).

4.5.2 Early compared to mid-stream samples

No studies were found comparing early to mid or late stream samples for any urine collection method in children.

4.5.3 Pad/nappy samples

A systematic review found four studies that examined the accuracy of specimens collected from pads/nappies. Three studies compared pad/nappy samples with culture of bag specimens, though bag collection was not considered likely to be the best method of urine sample collection, limiting the value of these studies. The remaining study was found to have compared the pad/nappy specimens to SPA samples, and reported 100% sensitivity and 94% specificity between the two methods. Limited data made it difficult to draw firm conclusions.[132][EL 2++]

An RCT conducted in the UK evaluated a modified urine collection pad method for its ability to reduce heavy mixed growth bacterial contamination of urine collection pad samples in 68 children (37 single pads, 37 replaced pads) children under 2 years old with suspected urinary tract infection.[133] Children were randomised into two groups: a single urine collection pad that was left in the nappy until a sample had been obtained; or a urine collection pad that was replaced every 30 minutes until a sample was obtained. Alarm sensors were placed in all urine collection pads. 80 children were recruited (42 in the single urine collection pad and 38 in the replaced urine collection pad), and urine collection failed in 12 children (5 single pad, 7 replaced pad) mainly because of faecal soiling of the pad and were excluded from the analysis.

Baseline characteristics of the groups were similar with respect to age, however there were significantly more boys in the single pad group (25/37 vs. 13/31, p=0.034)) 3/68 (4%) children had a UTI, mixed growth of $>10^5$cfu/ml was found in10/37 single pads compared to 1/31 replaced pads, mixed growth $<10^5$cfu/ml

was found in 3/37 single pads compared to 2/31 replaced pads and no growth was recorded on 22/37 single pads compared to 27/31 replaced pads. Of the remaining 65 who did not have a UTI, heavy mixed growth was significantly higher in the single pad (10/35), compared to the replaced pad (1/30) p=0.008.[EL 1+]

4.5.4 Bag samples

A systematic review[132] and three RCTs[134-136] investigated urine collection bags.

A systematic review found three studies examining bag specimens: one compared culture and microscopy results of bag specimens to catheter specimens, with sensitivity and specificity for both at 80%; the other two studies compared culture of bag samples with culture of SPA samples, with considerable difference in results – one reported a sensitivity of 100%, the other sensitivity of 50% - though both reported the specificity of around 90%. There was insufficient data for drawing firm conclusions about bag specimens.[132][EL 2++]

A cohort study conducted in the UK evaluated the ease of application and reliability of two different urine collection bags, the Hollister U-bags and the Urinicol bag in 50 children (33 boys, 17 girls) attending a children's clinic.[134]
The nurses first cleaned the genital area with warm tap water and cotton wool balls before applying the bag. Hollister U-bags were used in 18 boys and 7 girls,

while Urinicol bags were used in 15 boys and 10 girls. 8/25 Hollister u-bags leaked compared to 0/25 Urinicol bags (p<0.01)[EL 3]

A cohort study conducted in Canada compared the risks of contaminated culture results in urine specimens obtained by urine collection bag compared to catheterisation in 7584 urine samples were collected from 4632 children ≤24 months at an emergency department or outpatient unit.[135] Bag urine cultures were obtained by Hollister U-bag after the perineum was cleansed with antibacterial soap and tap water. In the outpatient centre the bag was replaced after 30 minutes, while in the emergency department it was not. Catheter specimens were only collected in the emergency department after cleansing with iodinated soap and sterile water

Of the 7584 urine cultures, 42.1% were obtained in infants <6 months, 25.9% in infants between 6 and 11 months and 31.9% from infants between 12 and 24 months. Of the bag specimens, 2597 were collected at the emergency department and 2530 at the outpatient unit. 2457 catheter specimens were collected at the emergency department. Bag collection (54.4% bag vs. 9.0 catheter (p<0.001)); male gender (38.7% male vs. 29.2% female (p<0.001)); and age over 12 months (31.4% <12 months vs. 38.7% 12-24 months (p<0.001)) were significantly more likely to be contaminated. Odds Ratio (adjusted for age, sex and leukocyte esterase test) was 13.3 (95%CI 11.3 to 15.6) and when limited to the first urine culture in each child was OR 13.6 (95%CI 11.1 to 16.7).[EL 2+]

A study conducted in the UK compared the contamination rates between bag and clean-catch urine collection methods in children under 2 years old in one of two inpatient wards.[136] In Ward A, the child's genitalia was washed with soap and water and urine samples were collected in a sterile foil bowl. In ward B soap and water was used, followed by cleansing with sterile water and drying with cotton wool balls and urine collection bags, either Hollister U-bags or Simcare bags were applied.

46 urine samples (23 from each ward) were obtained; in ward A 44 attempts were made to obtain 23 urine samples, 18 of which were obtained in one hour or less. A parent/carer was involved in 33 of the 44 attempts. Of the 11 times a nurse was involved, total time taken was 3 hours 25 minutes, however for 2 hours 15 minutes, nurses were also feeding the infants, therefore extra time taken overall was one hour 10 minutes. No specimens were contaminated

In ward B 28 attempts were made to obtain 23 samples. The urine collection bags were in place for 15 minutes to 4 hours 10 minutes, with an average time of one hour 25 minutes. 11 specimens were contaminated with faecal bacteria.[EL 3]

4.5.5 Catheter and SPA samples

A systematic review [EL2++] found one study showing good agreement between results of culture from early catheter specimens and late catheter samples, with

sensitivity of 100% and specificity of 95%. The limited data means that no further conclusions can be drawn.

A study conducted in Israel compared the severity of pain during SPA with pain during trans-urethral catheterisation in 51 infants (31 boys, 20 girls) younger than 2 months.[137] Pain during urine collection was assessed on a 100mm visual analog scale by a nurse and a parent/carer. Additionally, the infants upper body was video-taped during the procedure and an investigator assigned a point score based on the Douleur Aigue du Nouveaune (DAN) neonatal pain scale.

There were no baseline differences between children receiving SPA and those who were catheterised in terms of age or weight, however those who were catheterised were older than those receiving SPA (27.7 (±14.8) vs. 36.5 (±12.3), p=0.007). On the visual analog scale recorded by a nurse, the mean pain recorded for SPA was 63 (±18) compared to 43 (±25) for catheter. When parents/carers used the visual analog scale, they recorded a mean of 63 (±27) in children receiving SPA compared to 46 (±26) in children receiving catheter. Similarly, DAN scores and duration of cry were higher and longer for children randomised to SPA (7.0 (±1.9) and 62.9 seconds(±26) respectively) compared to infants randomised to catheter (4.5 (±2.1) and 49.7 (±35.7) respectively).[EL 2+]

4.5.6 Ultrasound guided SPA vs. Conventional SPA

Collecting urine from infants is difficult because they are unable to co-operate and therefore it is difficult to get an adequate clean catch sample. Supra-pubic aspiration has been regarded as the reference standard for urine collection in babies under 12 months of age, but is an invasive procedure with attendant risks and inexperienced clinicians can find this method difficult. Ultrasound guided SPA involves either scanning for the presence of urine before attempting an SPA, or scanning while aspirating the urine.

Four RCTs [138-141] were identified comparing ultrasound-guided SPA with conventional blind SPA.

An RCT conducted in Hong Kong investigated the optimal method of SPA in 60 infants, the success rate of real time ultrasound-guided SPA (30 infants; 19 boys, 11 girls) compared with conventional SPA (30 infants; 8 boys and 22 girls) and factors associated with success. [138] The overall success rates were 26/30 (87%) in the ultrasound guided group and 24/30 (80%) in the control group ($p<0.05$). The first attempts in both groups were equally successful 18/30 (60%). In the ultrasound-guided group compared with failed attempts, successful SPA was associated with a greater bladder depth (28 ± 11 vs. 21 ± 5, $p<0.01$), length (32 ± 12 vs. 23 ± 9, $p<0.05$) and volume (17 ± 13 vs. 8 ± 6, $p<0.01$) but similar width ($p>0.05$). In the control group, successful attempts were associated with the presence of bladder dullness demonstrated by light percussion (23/24 vs. 8/18, OR 29.0, $p<0.001$) compared with failed attempts.[EL 1+]

An RCT conducted in the USA investigated whether ultrasound guidance was useful to localise the position of the bladder and to increase the amount of urine obtained by SPA in 53 neonates.[139] 28 were randomized to the ultrasound-guided group and 25 to the control group. Ultrasound guided SPA was more likely to be successful on the first attempt (26/28 vs. 7/25, p=0.001); more successful overall – more than one attempt (27/28 vs. 15/25, p=0.003); have a greater volume of urine obtained (2.1 ± 1.2 vs. 1.3 ± 0.9, p=0.029); and require less passes (1.7 ± 1.0 vs. 4.4 ± 2.0, p=0.001). There were no differences with respect to procedure time (53 ± 59 seconds vs. 60 ± 40, p=0.600)[EL 1+]

An RCT conducted in the USA investigated whether portable ultrasound could improve the success rate of SPA in 66 children aged 0-15 months (median 1 month) presenting to a paediatric emergency department.[140] 15/19 (79%) of SPA attempts were successful in the ultrasound group compared to 16/31 (52%) in the control group (p=0.04). In 3/4 SPA attempts in the ultrasound group and in 11/15 SPA attempts in the control group, catheterisation yielded ≥5ml of urine. Operator efficiencies showed an increasing success rate over time (p=0.03)[EL 1+]

An RCT conducted in Turkey compared the success rates, number of attempts and volume of urine obtained as well as complication rates of SPA with or without ultrasound guidance in 140 infants (under 2 years).[141] 70 children were

randomised to the ultrasound-guided group (38 boys, 32 girls) and 70, controls (42 boys, 28 girls). Successful SPA was obtained in 63/70 (90%) of infants in the ultrasound guided group and 45/70 (64%) of the control group (p<0.05). Fewer attempts were necessary in infants in the ultrasound guided group (p<0.05).

In children under one month old, there were no differences in success rates between ultrasound guided (75%) and controls (74%) p>0.05. Additionally, the volume of urine obtained was approximately 6ml for both groups (p>0.05).[EL 1]

Table 4.5.6.1 Summary results for studies comparing ultrasound guided SPA with conventional methods

	[138]		[139]		[140]		[141]	
n	n=140		n=53		n=66		n=140	
	Ultrasound	**Control**	**Ultrasound**	**Control**	**Ultrasound**	**Control**	**Ultrasound**	**Control**
Numbers randomised	30	30	28	25	35 (SPA attempted in 19)	31	70	70
Success rate	87%	80%	96%	60%	79%	52%	90%	64%
Significance	p>0.05		p=0.003		p=0.04		p<0.05	

4.5.7 Early compared to late stream samples

A systematic review[132][EL 2++] found one study showing good agreement between the results of culture from early catheter samples and late catheter samples, with sensitivity of 100% and specificity of 95%. The limited data available means no firm conclusions can be drawn.

No other studies were found comparing early to late stream samples for any other urine collection method in children.

4.5.8 Other comparisons of urine collection methods

Four studies investigated other combinations of urine collection methods.[137;142-144]

A prospective cross-sectional study compared the validity of the urinalysis on clean-voided bag versus catheter urine specimens using catheter culture as the reference standard in non-toilet-trained children under 3 years old who presented to a children's emergency hospital in the USA between June 2000 and December 2001.[142]

The sensitivity of the bag dipstick was greater than the catheter dipstick (85% (95% CI 78% to 93%) vs. 71% (95%CI 61% to 81%) p=0.03) and sensitivity was highest in children >90 days. However, specificity of the bag dipstick for all ages was low compared with the catheter specimens (62% (95%CI 56% to 69%) vs. 97% (95%CI 94% to 99%) p<0.001). In the combined dipstick and microscopy urinalysis sensitivity of both bag and catheter specimens increased, and specificity decreased compared with dipstick alone.

The dipstick sensitivity in both bag and catheter samples did not differ according to sex, however specificity was higher in boys than in girls for all ages and could

not be explained by the fact that circumcision had been performed. Sensitivity rose with higher cut-off values for defining positive UTI, while specificity dropped.[EL III]

A study conducted in the USA compared bag and catheterised urine test performance characteristics in children aged under 93 days with temperature of 38°C or higher who underwent urinalysis and urine culture.[143]
Of the 1482 infants who had both urinalysis and urine culture, 1384 had samples obtained by bag or catheter. Overall, LE had higher sensitivity, while nitrites had higher specificity. The only significant difference between bag and catheter was the comparison of specificity of leukocyte esterase. There were no significant differences when the cut-off values for a positive result were changed.

Table 4.5.8.1 Summary measures[143]

	Leukocyte esterase		Nitrite	
Collection method	Sensitivity	Specificity	Sensitivity	Specificity
Bag	76%	84%	25%	98%
Pad	86%	94%	43%	99%
P value	0.19	<0.001	0.07	0.59

Further analysis of 54 patients who had false positive results for LE on bag urinalysis. Of the children who were also tested for nitrites, 4/1 (8%) had positive results. Of children who were also tested for urine white blood cell counts 9/47 (19%) had more than 10 WBC/hpf. If children who had urine samples with

positive LE and positive nitrite results, more than 10 WBC/hpf, or ambiguous culture results are considered to be positive for UTI, the difference between the methods in specificity for LE is still significant. (bag 89%, catheter 95%, p<0.001) The area under the ROC curve for urine WBC counts and UTI was higher in children with catheter samples than in those with bag samples (0.86 vs. 0.71, p=0.01). Catheter urine cultures provide a better sample for testing, however the difference is small.[EL III]

A study conducted in the UK assessed 44 parents/carers preferences for collecting urine at home from 29 boys and 15 girls aged 1 to 18 months and examined contamination rates.[144] Pads were placed inside the nappy and checked every 10 minutes until wet, then urine aspirated with a syringe. Bags were applied and inspected every 10 minutes and removed to decant urine. Parents/carers preferred using the pad first, the bag second and the clean catch method third. Seven samples from pads, eight from bags and one from clean catch had contamination.

Nine samples from 5 children grew $>10^5$ cfu/ml suggesting infection, however these were excluded by sterile samples collected on the same day in hospital.

Parents/carers found pads and bags easy to use and preferred them to the clean catch method. The pad was considered comfortable, whereas the bag was distressing, particularly on removal often leaking and leaving red marks. Some found extracting the urine from the pad or emptying the bag awkward. Most

parents/carers complained that the clean catch method was time consuming and often messy and nine parents/carers gave up after prolonged attempts.[EL 3]

Evidence summary

The urine collection methods that produce a most diagnostically accurate sample for testing are clean catch and SPA.

The only urine collection method for which there was an adequate amount of data was the comparison of clean voided urine to SPA. There were 5 studies 2 of which used different criteria for positivity.

When both samples were cultured the agreement between the methods was reasonable for NPV. One outlying study showed poor performance of clean voided urine. The reasons for this are unclear.

Ultrasound guided SPA is a more successful method of obtaining urine from the bladder than conventional SPA. Three of four studies found the use of ultrasound to detect urine in the bladder immediately before SPA increases the success rate of SPA.

There is insufficient data to draw conclusions about urine collection bags and urine collection pads. There is low level evidence that showed that the accuracy of urine collection pads was greatly improved if the pads were not used longer than 30 minutes.

Translation

If clean catch urine collection is not possible, urine collection pads are preferable to bags. In children who are not toilet trained, clean catch is often time consuming. Pads are less costly and cause fewer problems for the child than urine collection bags.

Recommendations

Clean catch urine sample is the recommended method for urine collection.

If a clean catch urine sample is unobtainable:

- Other non-invasive methods, such as urine collection pads should be used. It is important to follow the manufacturers instructions in using urine collection pads.
- When it is not possible or practical to collect urine by non-invasive methods, catheter samples or SPA should be used.
- If SPA is required, ultrasound guidance should be used to demonstrate the presence of urine in the bladder before SPA is attempted. This procedure should only be done by appropriately trained clinicians.

In an acutely unwell child it is highly preferable that a urine sample is obtained, however, treatment should not be delayed if a urine sample is unobtainable.

Cotton wool balls, gauze and sanitary towels should not be used to collect urine in children.

4.6 Urine preservation

Urine readily supports bacterial growth and specimens of urine are frequently contaminated. It is well recognised that time delays in culturing urine allows contaminants to multiply and produce inaccurate results. The addition of preservatives – usually boric acid – to the urine samples can be an alternative to lowering the temperature. Currently, boric acid is used in various commercially available transportation tubes.

When urine samples are currently requested, this is often with inadequate explanation of the collection procedure. Various studies have reported that this is a problem in primary care.

4.6.1 Chemical preservation

Six studies were found that evaluated chemical preservation of urine.[145-150]

One study in Sweden evaluated a commercial tube prepared with boric acid, sodium formate and sorbitol. One conventional tube was sent to the laboratory by ordinary chilled transport. Another conventional tube and one HG tube were transported to the laboratory without chilling. Cultures were performed upon arrival at the laboratory and then 24, 48 and 72 hours after primary sampling.

Of the 154 consecutive outpatients with suspected UTI, 144 had positive cultures, defined as $>10^6$ colony forming units (CFU) per litre. 24 hours after sampling there were no significant differences in bacterial counts between the chilled conventional tubes and the HG tubes at room temperature. However, in the HG tubes a significant change in enterococcal counts were noted after 48 hours.[145] [EL 2+]

One study in the USA evaluated whether or not chemical preservatives in the Becton-Dickinson urine culture kit had an effect on urinalysis, microscopy or Gram stain. Of the 304 clean-catch urine specimens obtained from pregnant women 2% had significant bacteriuria (10^5cfu/ml). There was complete agreement between preserved and unpreserved split samples in the detection of glucose, ketones, bilirubin and blood. Of the 388 women with symptoms of UTI seen in the emergency room or outpatients department 198 (51%) had significant bacteriuria.

Urine microscopy revealed a tendency for erythrocyte counts to be diminished after 24 hours at room temperature in unpreserved specimens. Gram stain

results of preserved and unpreserved split samples were comparable; staining characteristics were not altered by the preservative.[146][EL III]

One study in the UK compared methods of preservation with simulated specimens of pooled urine seeded with known five parallel comparisons of 6 species.[147] One strain each of *E.coli*, *Pseudomonas aeruginosa*, *Klebsiella aerogenes*, *Proteus mirabilis*, *Micrococcus* and *Streptococcus faecalis* were isolated from infected urine. An overnight culture of each test strain in pooled urine was serially diluted to give six simulated specimens of 10, 10^3, 10^4, 10^5, 10^6 and 10^7. In unpreserved specimens at room temperature each test strain multiplied rapidly and the surface viable counts showed concentrations of between 10^7 and 10^8cfu/ml within 72 hours in every specimen. In refrigerated specimens the surface viable counts for all the specimens remained constant for 72 hours. In specimens preserved with 1.8% boric acid, the surface viable counts remained constant for 24 hours, but he viable counts of specimens infected with *P.aeruginosa* fell markedly. After 24 hours the viable counts of the *E.coli* specimens, except for the most heavily infected specimen declined. The viable counts of specimens in the *Klebsiella aerogenes*, *Proteus mirabilis*, *Micrococcus* and *Streptococcus faecalis* and the specimen that was most heavily infected with E.coli remained constant for 72 hours. In specimens with 9% sodium chloride (NaCl) – 0.9% polyvinyl-pyrrolidone there were no differences between the results obtained with polyvinyl-pyrrolidone of the two molecular weights. The surface viable counts of all specimens of *E.coli* fell markedly within 24 hours,

except the viable count of the most heavily infected specimen which fell more slowly. The viable counts of the most heavily infected *K.aerogenes* remained constant while the other specimens fell more slowly. The strain of *Micrococcus* grew in the specimens however after 24 hours the viable counts remained in the same range that they were in at time zero. The viable counts of *Streptococcus faecalis* specimens remained constant for 72 hours, but the viable counts of all specimens in the *Proteus mirabilis* and *P.aeruginosa* specimens fell markedly within 24 hours.[EL 3]

One study in the USA evaluated the efficacy of collecting urine specimens in Becton-Dickinson tubes and subsequently screening them for bacteriuria with the Abbott MS-2.[148] Following collection, urine samples were immediately placed in the Becton-Dickenson tube and another in a screw-cap tube routinely used for transporting urine from the hospital to the laboratory. If samples could not be transported within 20 minutes, the conventional tube was refrigerated.

Of the 312 mid-stream urine specimens collected from obstetric outpatients receiving prenatal care, 124 were positive for bacteriuria. The median time required for urine specimens to be judged positive by the MS-2 was similar for conventional tube and for Becton-Dickenson tubes (95 and 105 minutes respectively). Bacterial specimen results from conventional tubes did not differ significantly from those from Becton-Dickinson tubes. Culture results from 24 hour delayed samples from the Becton-Dickinson tubes were significantly

different in that 40 of the 188 specimens had colony counts in excess of 10^5cfu/ml.[EL 3]

One study in the USA aimed to determine whether boric acid interferes with the reactions of the Chemstrip LN dipstick.[149] A preliminary study of Specimens negative for leukocyte esterase and nitrite were obtained by multiple mid-stream urine collections into disposable non-sterile urine cups from one asymptomatic volunteer male. Specimens positive for leukocyte esterase and nitrite were prepared by placing Chek-Stix urinalysis control strips in 12ml deionised water, following the manufacturers instructions. The positive and negative samples were then transferred to numbered Sage collection tubes containing boric acid. 21 samples (12 negative and 9 positive) were tested immediately following preparation and tested again after 2 hours. Preliminary studies with the LN+ and LN- samples preserved in boric acid demonstrated no evidence of interference with the LN strips immediately after preparation, or after the 2 hour incubation. Following the preliminary study, 177 consecutive clinical urine specimens from inpatients, outpatients and residents of a nursing centre preserved in boric acid were evaluated before routine culturing. The dipstick correctly indicated the presence or absence of nitrite and leukocyte esterase in all cases.[EL 2+]

One study in the USA evaluated the boric acid-glycerol-sodium formate preservative in the Becton-Dickinson urine culture kit and the use of ordinary paper cups for collection of urine.[150] Of 1000 urine samples from children and

adults with symptoms suggesting UTI and from pregnant women being screened for asymptomatic bacteriuria, 88 of the initial reference cultures were positive (pure growth of 10^5cfu/ml). 82 (93.2%) of the 88 specimens on reference culture were also positive after refrigeration or holding at room temperature in the transport tube for 24 hours. There was one false positive culture from refrigerated urine but none from the transport tube. Mixing urine in the non-sterile container did not introduce detectable contamination. [EL 3]

4.6.2 Temperature

Two studies were found that evaluated temperature for urine samples.[151;152]

One study in Costa Rica evaluated the effect of time, temperature and glucose content on the growth of two initial populations of either E.coli or P.vulgaris in sterile urine samples.[151] In urine containing no glucose, the original number of bacteria both in the urines and the controls showed little or no change over time. Populations of P.vulgaris remained unchanged at all three temperatures while E.coli showed a slight increase over time. In urine containing glucose all bacterial strains studied showed reductions in the populations after two hours of incubation at -10°C and continued to decline at 4 hours and 8 hours. However, there was a steady increase in bacterial numbers with time in the samples incubated at room temperature (25°C) which showed at least 10^5 organisms

within 4 hours. The bacterial populations showed almost no change when the incubation temperature was 4°C regardless of bacterial strain.[EL 3]

One study in the USA evaluated the minimum amount of urine necessary to obtain accurate results with the Sage urine culture tube and the Becton-Dickinson culture tube each system.[152] Both tubes were injected with 1, 2, 3 and 4-5 ml (tube capacity) of urine containing each culture. Specimens were held at 22°C and cultured at 0, 4 and 24 hours. The Becton-Dickinson urine culture kits were toxic to E.coli and Klebsiella pneumoniae in specimens containing up to 2ml of urine. The minimum useable amount of urine for reliable results was 3ml. The Sage urine culture tube maintained the number of bacteria in 1 to 4.5ml of urine in 83% of the specimens. However the Sage tube was toxic to E.coli when held for 24 hours. Quantitative counts of enterococci tended to significantly increase in specimens that contained 2ml or more of urine in either system. [EL 3]

4.6.3 Time

Two studies were identified that investigated the effect of time on the multiplication of bacteria in urine samples.[153;154]

One study from the UK investigated the multiplication of contaminant bacteria in urine and attempted to define the duration of delay during which bacterial culture

can be expected to give a reliable indication of the presence or absence of urinary infection.[153] Samples were collected from 106 patients attending a health centre and members of the hospital staff and cultures were performed within one hour of voiding and successive cultures were carried out at 2, 4, 8, 12 and 24 hours after voiding. Throughout the period of sampling, specimens were kept between 19°C and 23°C. In the freshly voided urine 14 of the 41 urine samples from males (34%) and 5 of 65 from females (7.7%) had bacterial populations of less than 10^2cfu/ml. None of the urines from males had bacterial counts in excess of 10^5cfu/ml, while four urines from females (6.2%) had counts exceeding 10^5cfu/ml. In subsequent cultures *Enterococci, E.coli, S albus* and group B *Streptococci* were the organisms which most commonly multiplied in urine to give counts in excess of 10^5cfu/ml within 24 hours of voiding. The lag phase was usually short and frequently indetectable. *Enterobacteria* other than *E.coli* were rarely isolated more than 10^2cfu/ml when sampling was carried out but at later samplings showed growth patterns similar to *E.coli*. All isolates grew exponentially after approximately 8 hours, and most had a lag time of approximately 4 hours. [EL 3]

One study in the USA evaluated the effect of transport delay on the micro flora of clinical specimens collected for microbiological analysis.[154] Clean catch urine specimens were collected from patients on medical wards and proportions of these specimens were cultures approximately 10 minutes after collection for aerobic organisms. The remainder of each specimen was kept at room

temperature until collected by the transportation service. The time necessary for transportation of the urine specimens ranged from 2 to 5 hours with an average of 4 hours. The results from 100 urine specimens cultured immediately after collection indicated that 71% had colony counts of less than 10^2; 14% between 10^4 and 10^5; and 15% more than 10^6. After transportation 71% maintained colony counts of less than 10^2; 9% between 10^4 and 10^5; and 20% more than10^6. [EL 3]

4.6.4 Refrigeration

Two studies investigated the effect of refrigeration on bacterial growth in urine samples.[155;156]

One study from the USA assessed the validity of overnight refrigeration for quantitative bacteriological evaluation and compared initial urine cultures (less than 2 hours old), with refrigerated urine cultures.[155] Of 414 urine cultures, there were 109 cultures with colony counts of 10^4cfu/ml or higher. Four cultures changed from sterile to significant colony count (10^5cfu/ml or greater), all of which were *S aureus*. There was also single culture which changed from 10^5cfu/ml to sterile where the organism involved was *E.coli*. Nine other cultures exhibited some change in colony count of which a number of organisms were involved in the discrepancies. [EL 3]

One study in the USA evaluated if bacterial concentrations generally considered insignificant (less than 10,000/ml) become significant as a result of bacterial multiplication in the urine during refrigeration.[156] Clean-catch specimens obtained from 'normal' males and females were refrigerated at 5°C for approximately 24 hours. The urine was then pooled, sterilized by pressure filtration and stored at 5°C in 100ml aliquots in sterile bottles. Two bottles were inoculated for each of the bacteria employed and the bottles were placed at 0.5°C, 5°C, 10°C and 15°C. Every 24 hours for 4 days samples of urine from each bottle were cultured. At 0.5°C, 5°C and 10°C, *E.coli* remained largely unchanged.

At 15°C, *E.coli* grew from 12,000/ml immediately after collection to 16,000/ml at 24 hours, 370,000/ml at 48 hours and reached 800,000/ml by 72 hours. Bacterial counts overall remained the most stable in the 5°C group. [EL 3]

Evidence summary

The studies included confirm the need for a method of preserving urine specimens when they cannot be examined immediately.

Culture of urine within four hours of voiding is likely to give a true indication of the presence or absence of bacteria. With further delay the interpretation of a heavy growth of bacteria in urine becomes progressively more unreliable. Where it is

impractical to culture urine within four hours, urine specimens which are to be used to detect bacteriuria should be refrigerated immediately following collection.

There is evidence to suggest that culture kits containing boric acid, sodium formate and sodium borate maintain a stable bacterial population in urine for up to 24 hours. However, prolonged storage (more than 24 hours) may alter subsequent bacterial counts. Potential toxicity against bacteria in the specimen from boric acid can occur if the manufacturers recommendations about the volume of urine required are not followed. There is no evidence that commercially available urine collection kits offer any advantage.

Recommendations

If urine cannot be cultured within four hours of collection the sample should be refrigerated or preserved with boric acid immediately on voiding.

When boric acid is used, manufacturers instructions should be followed to ensure correct specimen volume to avoid potential toxicity against bacteria in the specimen.

4.7 Urine testing

The prompt and accurate diagnosis of UTI is essential if this condition is to be managed correctly. The first step in making a diagnosis is to identify whether

children presenting to the healthcare system, often but not exclusively via primary care, have a UTI. The initial assessment will usually involve a combination of clinical assessment and diagnostic testing.

Diagnostic tests fall functionally into two groups. Firstly, those which give immediate results and secondly, those in which, due to the nature of the test there is a delay. Dipstick testing and microscopy fall into the first group and as such can assist in making an immediate assessment. Investigations involving bacterial culture fall into the second as an overnight incubation is required to allow bacteria to grow. The aim of this chapter is to review the evidence for the use of each test and make recommendations on how best to investigate a patient presenting with symptoms of UTI.

At present there is wide variation in practice. At one end of the spectrum all patients with possible UTI may be tested with a combination of dipstick and formal urine microscopy and culture. At the other end diagnostic testing may not be used until the patient has failed to improve following a course of empiric therapy. There is also wide variation both in the type of dipsticks used as a near patient test and in how microbiology laboratories perform microscopy and culture.

There are a large number of studies relating to diagnostic urine testing, however the majority of these studies did not recruit an appropriate patient group, patient selection criteria were poorly described and avoidance of biases was poorly

reported. Culture was used as a reference standard in the majority of studies but in others a combination of culture and microscopy was used. The cut off point for a positive culture was 10^5 colony forming units (cfu)/ml in most studies but in others cut offs of 10^3cfu/ml or 50,000cfu/ml were used. These differences meant appropriately comparable studies were limited.

Studies have clearly shown that the previously used cut of value of 10^5cfu/ml is arbitrary, a fact that was acknowledged by Professor Kass who founded the current criteria.

Bacterial counts as low as 1000cfu/ml can, in certain clinical situations, represent a true UTI but when bacterial numbers are lower, the chance of the identified bacteria representing contamination increases. In certain clinical situations mixed growth can also represent a real infection, for example when the infecting bacteria are “hidden” amongst a larger number of contaminating bacteria or in children with severe malformations in whom multi-bacterial infections occur.

The results from urine culture can therefore not be interpreted in isolation, but in relation to the clinical setting, symptoms and findings. The results of other diagnostic tests should also be considered.

4.7.1 Dipstick Urine Tests

Dipstick tests are a group of tests which involve dipping reagent strips into collected urine.

A systematic review identified 38 studies that evaluated dipstick tests for the diagnosis of UTI. The studies included dipstick tests for nitrite, leukocyte esterase, protein, glucose and blood.[132][EL 1++] A further meta-analysis identified 70 studies[157] and two additional studies were identified[158;159].

Nitrite

A systematic review reported 27 data sets from 23 studies investigating nitrite dipstick tests. [132] Culture was used as the reference standard in all but two studies where a combination of culture and microscopy was used as the reference standard. The majority of studies used 10^5cfu/ml as a positive reference standard. The studies reported poor sensitivity ranging from 16.2 (specificity 97.6%) to 88.1% (specificity 100%) and high specificity ranging from 75.6% (sensitivity 61.1%) to 100% (sensitivity 16.7 to 88.1%). Only two specificity estimates were below 90%. Positive likelihood ratios ranged from 2.5 (LR- = 0.51) to 439.6 (LR- = 0.63). Negative likelihood ratios ranged from 0.12 (LR+ = 157) to 0.86 (LR+ = 6.7). The pooled positive likelihood ratio was 15.9 (95%CI 10.7, 23.7) and the pooled negative likelihood ratio was 0.51 (95%CI 0.43, 0.60), however there was considerable heterogeneity in terms of likelihood ratios ($p<0.001$).[132][EL 1++]

Leukocyte esterase

A systematic review identified fourteen studies reporting 16 data sets which investigated leukocyte esterase dipstick tests.[132] Twelve studies used culture as the reference standard and two used a combination of culture and microscopy. Sensitivity ranged from 37.5% (specificity 96.4%) to 100% (specificity 92%). Specificity ranged from 69.3% (sensitivity 93.5%) to 97.8% (sensitivity 70%). Positive likelihood ratios ranged from 2.6 (LR- = 12.5) to 32.2 (LR- = 0.31). Negative likelihood ratios ranged from 0.02 (LR+ = 12.5) to 0.66 (LR+ = 6.97). There was considerable heterogeneity in both positive and negative likelihood ratios ($p<0.001$). The pooled positive likelihood ratio was 5.5 (95%CI 4.1, 7.3) and the pooled negative likelihood ratio was 0.26 (95%CI 0.18, 0.36).[132][EL 1++]

Protein

A systematic review identified two studies reporting three data sets that examined protein dipstick tests.[132] One study used culture and the other used a combination of culture and microscopy as the reference standard. The systematic review concluded that these studies did not use an appropriate spectrum of patients or adequately report the criteria used to select the patients. The studies did not report sufficient information to assess the avoidance of

review bias. The sensitivity was estimated to range from 8.1% (specificity 95.1%) to 53.3% (specificity 83.9%). Both studies found protein dipstick was a poor test for the identification of UTI.[EL 1++]

Glucose

A systematic review identified four studies containing five data sets investigating biochemical test strips for glucose using culture as the reference standard.[132] The studies identified investigated glucose strips which are not currently commercially available in the UK as currently available glucose strips are optimised to detect abnormally high urinary glucose levels.

Sensitivity ranged from 64% to 98% while specificity ranged from 96.4% to 100%. Positive likelihood ratios ranged from 27.8 (LR- = 0.07) to 166.2 (LR- = 0.02) while negative likelihood ratios ranged from 0.02 (LR+ = 166.2 and 113.7) to 0.36 (LR+ = 32.5). The pooled positive likelihood ratio was 66.3 (95%CI 20.0, 219.6) and the pooled negative likelihood ratio was 0.07 (95%CI 0.01, 0.83). There was significant heterogeneity in both the positive and negative likelihood ratios ($p<0.001$).[EL 1++]

Blood

A systematic review identified one study investigating the accuracy of dipstick tests for blood using culture as the reference standard.[132] The study reported that dipstick testing with blood is not a useful tool for diagnosing UTI in children with estimated sensitivities of 25.4% for visual examination and 53.3% for automated examination and specificities of around 85%. The systematic review concluded that the study did proved adequate information to evaluate if an appropriate spectrum of patients or to assess the avoidance of review bias.[EL 1++]

Leukocyte esterase or nitrite positive

A systematic review identified 15 studies containing 20 data sets examining the use of a combination test where either a positive leukocyte esterase dipstick or a positive nitrite dipstick was considered a positive UTI result.[132] All studies used culture as the reference standard. Sensitivity ranged from 69.4% (specificity 78.5%) to 100% (specificity 88.4%). Specificity ranged from 69.2% (sensitivity (94.1%) to 97.8% (sensitivity 70%). Positive likelihood ratios ranged from 3.0 to 32.2 while negative likelihood ratios ranged from 0.03 to 0.39. However likelihood ratios showed considerable heterogeneity ($p<0.001$). The pooled positive likelihood ratio was 6.1 (95%CI 4.3, 8.6) and the pooled negative likelihood ratio was 0.20 (95%CI 0.16, 0.26). [EL 1++]

Leukocyte esterase and nitrite positive

A systematic review identified 9 studies containing 12 data sets examining the use of a combination test where a positive result from both leukocyte esterase and nitrite dipstick was considered a positive UTI result.[132] All studies used culture as the reference standard.

Sensitivity ranged from 30% to 89.2%. Specificity ranged from 89.2% to 100% (sensitivity 30-88%). Positive likelihood ratios ranged from 8.0 to 197.1 while negative likelihood ratios ranged from 0.11 to 0.7 Both pooled positive and negative likelihood ratios were heterogeneous ($p<0.037$ and $p<0.001$ respectively). The pooled positive likelihood ratio was 28.2 (95%CI 15.5, 43.4) and the pooled negative likelihood ratio was 0.37 (95%CI 0.26, 0.52).[EL 1++]

Leukocyte esterase and protein positive

A systematic review identified one study investigating the use of a combination test where a positive result from both leukocyte esterase and protein dipstick was considered a positive UTI result.[132] A combination of microscopy and culture was used as the reference standard. The study reported a sensitivity of 89.2% and a specificity of 97.6%.[EL 1++]

Combinations of three dipsticks

A systematic review identified five studies reporting a total of 10 data sets, investigating various combinations of three dipsticks.[132] Four studies evaluated one combination of tests (nitrite, blood or protein positive; nitrite, blood or leukocyte esterase positive; nitrite, blood and leukocyte esterase positive; nitrite, leukocyte esterase or protein positive) and two further studies investigated the same combination (nitrite, leukocyte esterase and protein positive). All studies used culture as the reference standard.

Insufficient information was available to draw any overall conclusions, however one combination (nitrite, leukocyte esterase and protein positive) investigated by two studies appeared to be potentially useful for diagnosing UTI. One study reported a sensitivity of 96% and a specificity of 99%, while the second study reported a sensitivity of 89% and a specificity of 72%.[EL 1++]

A meta-analysis of urine dipstick tests to rule out infection identified 70 studies.[157] Accuracy of nitrites was higher in pregnant women (Diagnostic odds ratio (DOR) = 165) and in elderly people (DOR = 108). Positive predictive values were ≥80% in elderly and in family medicine. Subgroup analysis of diagnostic accuracy found ten studies of nitrite dipstick tests in children. Sensitivity was 50% (42% to 60%), specificity 92% (87% to 98%) with a DOR 34 (12, 97). Accuracy of leukocyte esterase was high in studies in urology patients (DOR = 267). Negative predictive values were high in both tests in all patient groups and settings except in family medicine. The combination of both test results showed an increase in sensitivity. Accuracy was high in studies in urology patients (DOR = 52), in

children (DOR = 46) and if clinical information was present (DOR = 28). Predictive values of combinations of positive test results were low in other situations. Subgroup analysis of accuracy of nitrite and leukocyte esterase dipsticks in combination found nine studies of nitrite dipstick tests in children. Sensitivity ranged from 78% to 89% and specificity ranged from 79% to 91% with a DOR 46 (23, 95). Using a pre-test probability (prevalence) of 0.20, based on the pooled sensitivities and specificities of the studies are as follows: for nitrites alone the PPV in children was 61% and the NPV 88%; for leukocyte esterase alone the PPV in children was 34% and the NPV 88%; for one or both dipsticks positive, the PPV in children was 58% and the NPV 95%; for both dipsticks positive, the PPV in children was 66% and the NPV 87%.[EL II]

One study investigated whether dipstick urinalysis for leukocytes, nitrites, blood and protein in the paediatric population is an adequate screening tool to exclude UTI.[158] Prevalence of UTI overall was calculated to be 10.7% in a paediatric population with a higher prevalence (15%) in children under 2 years, and lower prevalence in children 2-10 years (7%). The sensitivity of the dipstick in all cases was 92.5% (95%CI 84.3 to 100%), specificity 39.4% (95%CI 34.2 - 44.6%), positive predictive value 15.4% (95%CI 10.8 - 20%) and negative predictive value 97.8% (95%CI 95.3 to 100%). The sensitivity of the dipstick in children aged 0-2 years was 87.5% (95%CI 74.3 to 100%), specificity 39.7% (95%CI 31.5 to 47.9%), positive predictive value 20.4% (95%CI 12.6 to 28.2%) and negative predictive value 94.7% (95%CI 88.9 - 100%). The sensitivity of the dipstick in

children aged 2-10 years was 100% (95%CI 100 - 100%), specificity 39.2% (95%CI 32.4 to 46%), positive predictive value 11.0% (95%CI 5.8 to 16.3%) and negative predictive value 100% (95%CI 100 - 100%). [EL II]

One study assessed the clinical utility of pathogen-specific tests to be applied with widely used dipsticks.[159] Combination of leukocyte and nitrite dipsticks gave negative predictive values of 93% for culture-negative samples. Using the same dipsticks on culture positive samples, the positive predictive values were unacceptably low. The false negative rate for leukocyte esterase or nitrite dipstick tests was 5% (80/1743), false positive rate 17% (304), True positive rate 15%(262) and true negative rate 63% (1097). The positive predictive value was 46% and the negative predictive value 93%.

The false negative rate for the immuno-chromatography strip was 10% (168/1743), false positive rate 2% (42), True positive rate 10% (174) and true negative rate 78% (1359). The positive predictive value was 81% and the negative predictive value 89%. The false negative rate for combination leukocyte esterase, nitrite dipstick and immuno-chromatography tests was 11% (190/1743), false positive rate 1% (19), True positive rate 9% (152) and true negative rate 79% (1382). The positive predictive value was 89% and the negative predictive value 88%.[EL II]

Evidence summary

Significant heterogeneity exists between studies making it difficult to draw overall conclusions about urine dipstick tests. However it is clear that leukocyte esterase and nitrite dipsticks are more valuable in diagnosing UTI used in combination than when they are used alone. There is general agreement among studies that a combination of a positive nitrite with positive leukocyte esterase has the highest positive likelihood ratio and is the most useful dipstick test for ruling in UTI. However a negative result for either nitrite or LE has the highest negative likelihood ration and will be most useful in excluding UTI.

Glucose dipstick tests may be useful for both ruling in and ruling out UTI, however evidence is limited.

There is not enough evidence to draw conclusions about dipstick tests for protein, blood or combinations of three or more dipstick tests.

4.7.2 Microscopy

The performance and interpretation of microscopy is more demanding than dipsticks and a variety of cellular elements can be identified in urine, white cells, red cells, bacteria, casts, by a number of different microscopic methods including Inverted microscopy, gram stain, centrifuged deposit

Pyuria

A systematic review reported 28 studies (49 data sets) investigating the microscopic detection of pyuria. 25 studies used culture as the reference standard, three studies used culture and automated microscopy. Only half the studies included an appropriate spectrum of patients and ten studies did not provide an adequate description of patient selection. Most studies did not provide enough information to assess the avoidance of review bias. One third did not provide an adequate description of the test and/or the reference standard. Several studies reported results for different cut-off points.

Sensitivity ranged from 36.6% to 96%. Specificity ranged from 31.5% to 100%. Positive likelihood ratios ranged from 1.3 (LR- = 0.33) to 27.7 (LR- = 0.09). Negative likelihood ratios ranged from 0.04 (LR+ = 24.0) to 0.68 (LR+ = 5.3). Likelihood ratios showed considerable heterogeneity ($p<0.001$). The pooled positive likelihood ratio was 5.9 (95%CI 4.1 to 8.5) and the pooled negative likelihood ratio was 0.27 (95%CI 0.20 to 0.37).

ROC curves suggested that the considerable heterogeneity between studies was not just the result of cut-off values but was likely to be caused by other factors. Regression analysis indicated that centrifugation of the sample, description of selection criteria, test bias, review bias, description of study withdrawals and age were significantly associated with the heterogeneity observed. Multivariate analysis showed that only two items remained significant; centrifugation of the sample and reporting selection criteria. The DOR was 0.2 times less in samples

centrifuged compared with non-centrifuged samples and three times greater in studies that provided an adequate description of selection criteria.[132][EL 1++]

Bacteriuria

A systematic review reported 22 studies (including 34 data sets) evaluating the microscopic detection of bacteriuria. Nineteen studies used culture as the reference standard. One study used culture and microscopy as the reference standard and a further two studies used culture and automated microscopy as the reference standard. Approximately half did not include an appropriate spectrum of patients, eight studies did not provide selection criteria, only four studies reported blinding. One third of studies did not provide adequate descriptions of the test and/or reference standard.

Sensitivity ranged from 52.4% to 100% and specificity ranged from 40% to 99.7%. Positive likelihood ratios ranged from 1.6 to 304.8 and negative likelihood ratios ranged from 0.01 to 0.48. Likelihood ratios showed considerable heterogeneity ($p<0.001$). The pooled positive likelihood ratio was 14.7 (95%CI 8.7 to 24.9) and the pooled negative likelihood ratio was 0.19 (95%CI 0.14 to 0.24). ROC curves indicate that although different cut-off points may account for some of the heterogeneity, it is likely that other factors may be contributing to test performance. In univariate regression analysis gram stain and incorporation bias were shown to be significant and both remained significant in multivariate

analysis. The DOR was 5.5 times greater in samples that were gram stained and in studies where incorporation bias was not present, the DOR was 100 times greater.[132][EL 1++]

One study compared the accuracy in diagnosing significant bacteriuria between quantitative unspun-urine microscopy and the gram-stain method.[160] Significant bacteriuria was detected by urine culture in 37 out of 325 urine samples. Unspun-urine microscopy samples in cell-counting chambers were negative in 248 samples, positive in 33 and ambiguous in 44. Ambiguous samples were subjected to oil-immersion microscopy which made it possible to identify rods, cocci, salts or other particles. Overall, unspun-urine microscopy was able to detect bacteriuria in 35 of 37 urine samples with culture-proven significant bacteriuria (sensitivity 94.6%), failing to identify bacilli in two urine samples. Unspun-urine microscopy identified 286 of 288 urine samples with negative culture results (specificity 99.3%). Gram-stain method was able to detect bacteriuria in 33 of 37 urine samples with culture-proven significant bacteriuria (sensitivity 89.2%). Gram-stain method identified 284 of 288 urine samples with negative culture results (specificity 98.6%). Both the unspun microscopy and the gram stain methods were similarly reliable when compared with culture. [EL II]

One study compared the accuracy of the differential fluorescent staining method and the gram stain method in screening for bacteriuria to conventional culture.[161] A total of 1487 urine samples were tested. 289 were found to have colony

counts greater than 10^4cfu/ml; 237 yielded a single organism and 52 a mix of two or more organisms.

Of the 237 yielding a single organism 224 were detected by the differential fluorescent staining method and 162 by the gram stain (13 undetected by the differential fluorescent staining method and 75 undetected by the gram stain).

The sensitivity of the differential fluorescent staining method was 94.5% while the sensitivity of the gram stain was 68.3%. The specificity of the differential fluorescent staining method was 91.6% and the gram stain 75.8%. The PPV and the NPV of the differential fluorescent staining method were 67.6% and 98.8% respectively and those of the gram stain 35.9% and 92.3%. [EL III]

Pyuria or bacteriuria

A systematic review reported 8 studies (including 10 data sets) investigating combinations of pyuria or bacteriuria where a positive result from either test was taken as a positive result for UTI.[132] More than half of the studies did not include an appropriate spectrum of patients, and the majority did no provide adequate information to assess the avoidance of test review bias (blinding). Sensitivity ranged from 75% to 100% and specificity ranged from 32.3% to 92.9%. Positive likelihood ratios ranged from 1.5 to 12.9. Negative likelihood ratios ranged from 0.02 to 0.27. Likelihood ratios showed considerable heterogeneity ($p<0.001$). The pooled positive likelihood ratio was 4.2 (95%CI 2.3 to 7.6) and the pooled negative likelihood ratio was 0.11 (95%CI 0.05 to 0.23). ROC curves indicate

that the considerable heterogeneity between studies is not just the result of different cut-off points but is likely to be caused by other factors. There was insufficient data to investigate heterogeneity further using regression analysis. [EL 1++]

Pyuria and bacteriuria

A systematic review reported 8 studies (including 10 data sets) investigating combinations of pyuria and bacteriuria where a positive results from both test was taken as a positive result for UTI.[132] All studies used culture as the reference standard. The majority of studies included an appropriate spectrum of patients, although did not provide adequate information to assess test review bias (blinding).

Sensitivity ranged from 46.7% to 93.1% and specificity ranged from 73.6% to 99.7%. Positive likelihood ratios ranged from 2.7 to 281. Negative likelihood ratios ranged from 0.07 to 0.56. Likelihood ratios showed considerable heterogeneity ($p<0.001$). The pooled positive likelihood ratio was 37.0 (95%CI 10.9 to 125.9) and the pooled negative likelihood ratio was 0.21 (95%CI 0.13 to 0.36). ROC curves indicate that the considerable heterogeneity between studies is not just the result of different cut-off points but is likely to be caused by other factors. There was insufficient data to investigate heterogeneity further using regression analysis. [EL 1++]

Evidence summary

Given the heterogeneity between studies and the lack of data for combinations of microscopy tests, it is difficult to draw overall conclusions about the diagnostic accuracy of microscopy for detecting UTI. However the pooled likelihood ratios show that a negative result for either pyuria or bacteriuria (LR- 0.11 95% CI 0.05-0.230) is better at ruling out UTI than dipstick testing.

A systematic review concludes that bacteriuria is considerably better than pyuria for ruling in and ruling out UTI. The diagnostic performance of bacteriuria may be improved when combined with pyuria, but there is insufficient evidence to provide certainty in these estimates.

4.7.3 Culture

A systematic review reported 9 studies investigating the accuracy of culture for the diagnosis of UTI.[132] Eight studies examined dip-slide cultures and one study compared standard culture to a reference standard of culture and microscopy combined. Studies were generally of poor quality and poorly reported. More than half did not use an appropriate spectrum of patients, did not report selection criteria and did not provide an adequate description of the test and/or reference

standard. The majority of studies did not provide adequate information to assess test review bias (blinding).

Sensitivity ranged from 56.3% to 100% and specificity ranged from 70.7% to 100%. Positive likelihood ratios ranged from 2.7 to 135.4 and negative likelihood ratios ranged from 0.02 to 0.46. There was considerable statistical heterogeneity in both positive and negative likelihood ratios ($p<0.001$) The pooled positive likelihood ratio was 14.6 (95%CI 6.7 to 31.8) and the pooled negative likelihood ratio was 0.23 (95%CI 0.14 to 0.39). ROC curves indicate considerable heterogeneity across the studies with no clear outliers. There were not enough studies to investigate heterogeneity further using regression analysis. [EL 1++]

One study assessed the validity of urine dip slides performed under daily practice conditions and assessed the influence of the incubation period (24 v 48 hours) on validity.[162] The nitrite test was the initial test in all practices. Of the 268 urine samples a sensitivity of 42% (95%CI 34 to 49%) and a specificity of 95% (95%CI 89 to 98%) was reported. The PPV was 93% (95%CI 85 to 98%) and the NPV 50% (95%CI 42 to 57%). The sensitivity of the dipslide in general practice after 24 hours incubation was 73% (95%CI 66 to 80%) and specificity was 94% (95%CI 88 to 98%). The PPV was 95% (95%CI 90 to 98%) and the NPV 68% (95%CI 60 to 76%). As the dipslide is only recommended in the case of a negative nitrite test, when performed after a negative nitrite test the PPV was 92% (95%CI 84 to 98%) and the NPV 73% (95%CI 64 to 81%). Overall the

dipslide read under practice conditions performed less well than when performed under optimal conditions. [EL II]

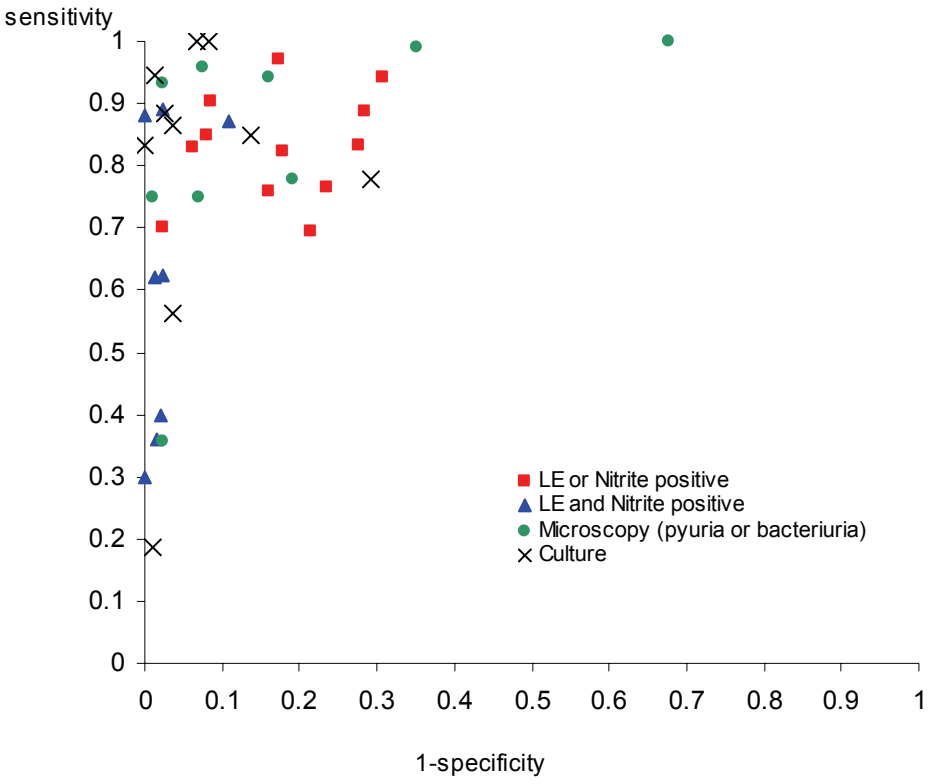
One study evaluated the diagnostic performance of the DipStreak device (using two different medium formulations) compared to Uriselect 3 plates and the reference streak method (calibrated loop).[163] In the study comparing Dipstreak (CHROMagar and MacConkey media), Uriselect 3 plates and calibrated loop culture, 2000 urine samples were processed and 511 cultures were found to be positive. The CHR dipstreak device, the Uriselect 3 and calibrated loop cultures gave the same detection rate (99.7%). For the direct identification of E.coli, Proteus and Enterococcus isolates, the DipStreak device and Uriselect showed overall sensitivities of 97% and 93.4%. In the second study comparing Dipstreak Uriselect 3 and MacConkey media, 3000 urine samples were processed and 714 cultures were found to be positive. The DipStreak device, the Uriselect 3 and calibrated loop cultures gave detection rates of 99.4%, 99.9% and 99.2% respectively. For the direct identification of E.coli, Proteus and Enterococcus isolates, the DipStreak device and Uriselect plates showed overall sensitivities of 88.7% and 94.4% respectively. [EL III]

Evidence summary

There is not enough evidence to draw conclusions about different methods of culture for detecting UTI in children. The pooled negative likelihood ratio for

culture is 0.23 which shows that culture is no better for ruling out UTI than dipstick testing for leukocyte esterase or nitrite or microscopy for pyuria or bacteriuria. As culture and microscopy are no more accurate than a dipstick testing for leukocyte esterase or nitrite, they cannot be considered cost-effective.

Table 2.7.3.1 LE or nitrite dipstick, microscopy and culture plotted in ROC space



4.7.4 Combinations of two or more methods

A meta-analysis of urine screening tests for UTI in children concluded that rapid dipstick tests could not be definitively assessed because of the small number of studies assessing their effectiveness. Bivariate summary ROC (SROC) curves showed that pyuria ≥10/hpf *and* bacteriuria ≥10/hpf had the best diagnostic performance. -+In multivariate analysis, both remained significant.[164][EL II]

One study evaluated the diagnostic properties of urine gram stain and urine microscopic examination for screening UTI. The prevalence of UTI from culture was 54.7% (52 cases).[165] The sensitivity of the Gram stain was 96.2%, specificity 93.0%, positive predictive value 94.3% and negative predictive value 95.2%. The sensitivity of the microscopic examination was 65.4%, specificity 74.4%, positive predictive value 75.6% and negative predictive value 64.0%. Combining the Gram stain and the microscopic examination, the sensitivity was 98.1%, specificity 74.4%, positive predictive value 82.3% and negative predictive value 97.0%. [EL Ib]

One study aimed to determine which method best identified UTI in children under 5 years presenting to a paediatric emergency department.[166] 25 cases (17.6%) of UTI were diagnosed by culture, 48% were ≤12 months and 16% were male. Positive leukocyte esterase dipstick had an overall sensitivity of 48% and a negative predictive value of 90%. In children ≤12 months, sensitivity was 42% while in children over 12 months, sensitivity was 53%. Positive nitrite dipstick had

an overall sensitivity of 20% and a negative predictive value of 85%. In children ≤12 months, sensitivity was 17% while in children over 12 months, sensitivity was 23%. Positive blood dipstick had an overall sensitivity of 44% and a negative predictive value of 88%. In children ≤12 months, sensitivity was 33% while in children over 12 months, sensitivity was 53%. Positive unspun leukocyte count >10/µl had an overall sensitivity of 68% and a negative predictive value of 92%. In children ≤12 months, sensitivity was 67% while in children over 12 months, sensitivity was 69%. Positive cyto-centrifuge Gram stain had an overall sensitivity of 60% and a negative predictive value of 92%. There was a statistically significant difference between children ≤12 months (sensitivity 42%) and children over 12 months (sensitivity 76%) ($p<0.05$). 2 to 5 or more leukocytes/hpf in sediment had an overall sensitivity of 48% and a negative predictive value of 90%. In children ≤12 months, sensitivity was 42% while in children over 12 months, sensitivity was 53%. [EL II]

One study compared the performance of leukocyte esterase and nitrite dipstick with the assessment of pyuria by microscopic examination and culture of urine samples in patients with symptoms of UTI.[167] The sensitivity of the leukocyte esterase dipstick was 68.4%, specificity 73.4%, positive predictive value 43.7% and negative predictive value 88.5%. The sensitivity of the nitrite dipstick was 58.9%, specificity 77.8%, positive predictive value 60% and negative predictive value 86.2%. The sensitivity of the microscopic pyuria count was 34%, specificity 86.5%, positive predictive value 43.5% and negative predictive value 81.3%.

There was a significant correlation between dipstick results, microscopic examination and urine culture (p=0.0001). [EL III]

One study investigated the validity of the urinary Gram stain compared with a combination of pyuria plus Gram stain and overall urinalysis.[168] Of the 100 children, 70% had a positive urine culture. The sensitivity of the Gram stain was 80%, specificity 83%, positive predictive value 91% and negative predictive value 64%. The sensitivity of the combination of Gram stain and pyuria was 42%, specificity 90%, positive predictive value 90% and negative predictive value 40%. The sensitivity of the overall urinalysis was 74%, specificity 3.5%, positive predictive value 64% and negative predictive value 5%. The study concluded that neither method (Gram stain, or Gram stain plus pyuria) should substitute for urine culture in symptomatic children. [EL III]

Evidence summary

There is not enough evidence to draw conclusions about combinations of methods for detecting UTI in children and they cannot be considered cost-effective.

4.7.5 Other tests

A systematic review identified 6 studies that examined other tests for the diagnosis of UTI.

A study published in 1968 examined the triphenyl-tetrazolium chlorine reduce (TCC) test and the Greiss nitrate reduction test.[132] One study evaluated three laboratory based blood tests (peripheral WBC, ESR and c-reactive proteins) in which all were found to be poor tests for diagnosing UTI. Other tests included FiltraCheck-UTI for bacteriuria, quantitative estimation of proteinuria and two studies of Uriscreen (reporting contrasting results). Only one study used an appropriate spectrum of patients and only two reported an adequate description of the test and/or the reference standard. Because of the small number of studies that examined these tests, there was insufficient information to assess their usefulness in diagnosing UTI. [EL 1++]

One study evaluated the analytical performance of the Sysmex UF-100 cytometer compared to culture for diagnosing UTI.[169] Of the 2010 patients considered, 529 (26.3%) had a UTI. Of the dipstick screening tests (Nitrite and leukocyte esterase dipstick tests) 171 (8.5%) false negatives were observed and 184 (9.2%) false positives. Sensitivity was 0.64 and specificity of 0.88 while PPV was 0.63 and NPV was 0.89. Of the culture tests (bacterial growth on CLED agar) 56 (2.8%) false negatives were observed and 35 (1.7%) false positives sensitivity was 0.89 and specificity of 0.98 while PPV was 0.93 and NPV was 0.89. Of the UF-100 tests 29 (1.4%) false negatives were observed and 102 (5.1%) false positives. Sensitivity was 0.94 and specificity of 0.93 while PPV was

0.83 and NPV was 0.98. The sysmex UF-100 performed more accurately than both the dipstick testing and culture. [EL II]

Evidence summary

There is not enough evidence to draw conclusions about alternative diagnostic tests for identifying UTI in children.

4.7.6 Diagnostic criteria for UTI

One study conducted in a laboratory aimed to determine if the biochemical results of the urine dipstick could be used to eliminate unnecessary urine cultures.[170] Of the 6192 urine samples processed, 64% (3932) had cultures performed. These were samples which showed positive dipstick and were ordered on physician request, or were not cancelled. 36% (2260) had a negative dipstick and were cancelled. The rate of cancellation appeared consistent at approximately one third when tracked month by month. Of the 3932 samples cultured 22.4% (883) were true positives (positive dipstick and positive culture), while 31.8% (1248) had a positive dipstick but grew organisms that were considered contaminants. False positive results were observed in 1558 (39.6%). Of the samples that showed negative dipstick and were cultured 11 (0.3%) grew a clinically significant pathogen. The study concluded that the biochemical parameters on urine dipsticks can be used as a screen to determine whether or

not a urine culture should be performed and implementation of this policy has resulted in the elimination of up to one third of the urine cultures performed in one laboratory. [EL III]

A second study conducted in a laboratory investigated whether dipstick or microscopy results reliably predicted the presence or absence of a reportable urinary pathogen.[171] There were 266/500 (53%) specimens with no growth and 77 (15%) had pure growth of a pathogen. The sensitivity of detecting pyuria on microscopy to predict the presence of a pathogen was 63%, specificity 89%, positive predictive value 58% and negative predictive value 91%. The sensitivity of detecting haematuria on microscopy to predict the presence of a pathogen was 18%, specificity 89%, positive predictive value 27% and negative predictive value 82%. The sensitivity of detecting squamous epithelial cell contamination on microscopy to predict mixed culture was 34%, specificity 89%, positive predictive value 53% and negative predictive value 78%. The sensitivity of detecting negative microscopy (no WBCs or squamous epithelial cells) to predict the absence of a pathogen was 76%, specificity 74%, positive predictive value 92% and negative predictive value 74%. The sensitivity of a negative dipstick to predict the absence of a pathogen was 83%, specificity 76%, positive predictive value 94% and negative predictive value 76%. The sensitivity of a negative dipstick and negative microscopy to predict the absence of a pathogen was 68%, specificity 85%, positive predictive value 95% and negative predictive value 85%.

Overall, the presence of haematuria or squamous epithelial cells were poor predictor of specimens with mixed cultures. The absence of pyuria had a reasonable negative predictive value (91%) for the presence of a pathogen. Negative microscopy had an adequate positive predictive value (92%), as did negative dipstick (94%). The combination of negative microscopy and dipstick (95%) did not significantly increase the ability to detect a pathogen. [EL III]

One study investigated the sensitivity of the standard urinalysis as a screening test for UTI in 11089 patients who had urine cultured to determine how it varies with age and to determine the clinical situation that necessitates the collection of urine culture regardless of the urinalysis result.[172] The study found that sensitivity of urinalysis was 82% (95%CI 79-84%) and did not vary with age. The specificity of urinalysis was 92% (95%CI 91-92%). The positive likelihood ratios was 10.6 (95%CI 10.0 to 11.2) and the negative likelihood ratio was 0.19 (95%CI 0.18 to 0.20). (n=11089 patients with urine cultures obtained) [EL III]

A study conducted in China evaluated the usefulness of catheter urine cultures in diagnosing symptomatic UTI in 492 uncircumcised boys compared to 460 girls aged 1 to 18 months (mean age 0.49 years) who had catheter urine cultures performed between July 1999 and June 2002 at a paediatric hospital and to test whether a single cut-off bacterial count has high sensitivity and specificity.[173] Children were classified as group A if they had a positive urine catheter culture, acute fever, positive LE and Nitrite dipstick and leukocytes on microscopy, and a

definite response to antibiotic treatment; and group B if they had cultures yielding no growth, urine culture positive but asymptomatic and had negative urinalysis results. Group A were used as the gold standard.

There were significantly higher counts in group A children than group B ($p<0.001$) and group B had significantly more cases of mixed growth ($p<0.001$). The probability of UTI was increased when CFU/ml was >105 for uncircumcised boys (LR 20.2) and >105 (LR 18.8) or 104 – 105 (8.95) for girls. UTI was unlikely when CFU/ml were 100-103 (LR 0.11) or 103 – 104 (LR 0.45) for boys or if mixed growth was found (LR 0.21, 95%CI 0.12 to 0.37).[EL III]

Translation

When examining the evidence and formulating a recommendation there are three areas to be considered.

1. Which is the most diagnostically accurate test
2. Is this test likely to give problems in terms of it's applicability or reproducibility
3. How applicable is the test to the population in which it will be used.

The absolute accuracy of the tests overall is summarised in table below

Table 4.7.6.1 Summary accuracy of urine tests

Type of test	+ LR (95% CI)	-LR (95% CI)
Nitrite	15.9 (10.7-23.7)	0.51 (0.43-0.6)

LE	5.5 (4.1-7.3)	0.26(0.18- 0.36)
LE OR Nitrite	6.1 (4.3-8.6)	0.2 (0.16-0.26)
LE AND Nitrite	28.2 (15.5-43.4)	0.37 (0.26-0.52)
Pyuria	5.9 (4.1-8.5)	0.27 (0.2-0.37)
Bacteriuria	14.7 (8.7-24.9)	0.19 (0.14-0.24)
PyuriaORbacteriuria	4.2 (2.3-7.6)	0.11(0.05-0.23)
Pyuria AND bacteriuria	37 (10.9-125.9)	0.21 (0.13-0.36)
Culture	14.6(6.7-31.8)	0.23 (0.14-0.39)

It is clear from the data that the tests best for ruling out UTI are either a combination of LE *or* Nitrite positivity on dipstick or the presence of pyuria or bacteriuria on microscopy. The tests best suited to rule in UTI are a combination of LE *and* Nitrite on dipstick testing or a combination of pyuria and bacteriuria on microscopy. A likelihood ratio (LR) of >10 is usually taken to mean a large and often conclusive increase in the likelihood of disease. The dipstick tests Nitrite, LE *and* Nitrite and the microscopy tests Bacteriuria *and* Pyuria meet this criteria but due to the heterogenous nature of the likelihood ratios only in studies of Nitrite, LE *and* Nitrite and Bacteriuria *and* Pyuria do all the studies have LR>10. In terms of negative LR < 0.1 is taken as a large and often conclusive decrease in the likelihood of disease with <0.2 indicating useful diagnostic evidence. So although LR's of greater than 0.1 may not be regarded as strong evidence it is the reduction of pre-test probability to an acceptable post test probability of around 5% (St John Review), When the results of all studies of dipsticks are plotted using Bayes theorem the post-test probabilities as a rule out test tend to

be small with most studies <0.05. Applying the same analysis to the the use of LE or Nitrate as a rule in test several studies do not achieve a post test probability of 95% As such there is better evidence to use LE OR Nitrite as a rule out strategy rather than a rule in strategy The next thing to consider is whether the test is likely to give problems in its applicability or reproducibility.

In terms of reproducibility it is widely recognised that microscopy is operator dependant and may be difficult to offer routinely as a near patient test in the primary care sector. Although the mean LR- of microscopy for pyuria and bacteriuria is less than LE or Nitrite dipstick testing in the worst performing studies there is little difference so the difficulty and variability of microscopy is unlikely to make much difference in terms of outcomes.

The final factor to consider is how applicable is the test to the population in which it will be used. One of the studies above[158] shows how test performance can vary with the prevalence of disease which is related to the age of the child. The amount of Nitrite and number of bacteria are likely to depend upon the amount of time that urine stays in the bladder. Thus the performance of both dipstick tests and urine culture will probably depend on bladder physiology. While the evidence shows that the NPV of dipstick tests is 100 in age 2-10 there is an age below 2 where the evidence is less clear.

The evidence for urine testing in younger children is limited and therefore the GDG has made the following recommendation regarding the age cut off of 3 on

the basis that based on consensus to diagnose UTI by urine culture rather than by dipstick test.

The two parameters measured by the dipsticks can be interpreted separately. The positive likelihood ratio for nitrite was 15.9 compared with 5.5 for leukocyte esterase. This means that a positive nitrite is more likely to indicate the presence of bacteria in the urine. Leukocyte esterase may be positive when infections outside the urinary tract are present.

A positive nitrite dipstick alone is more likely to indicate a urinary tract infection than a positive leukocyte esterase dipstick alone.

Recommendations

In children aged three years or over, combined nitrite and leukocyte esterase dipstick tests are recommended to diagnose urinary tract infection.

In children under the age of three years urine should be sent for microscopy and culture to diagnose urinary tract infection.

Table 4.7.6.2 Dipstick results and UTI diagnosis

Urine Dipstick	Diagnosis
Nitrite and LE positive	UTI – treat with antibiotics
Nitrite positive and LE negative	Probable UTI – treat with antibiotics
Nitrite negative and LE positive	May or may not be UTI – management should be based on

	clinical judgment
Nitrite and LE negative	UTI Excluded – no antibiotic treatment

Dipstick testing is no less accurate than microscopy in children over the age of three years but is less operator dependent and less costly therefore Microscopy is not routinely recommended for diagnosing urinary tract infection in older children.

Urine samples should not be routinely sent for culture in children over the age of three years with first time urinary tract infection who have a urine dipstick which is negative or positive for both nitrite and leukocyte esterase.

Urine samples should be sent for culture in:

- Systemically unwell children of all ages
- All children under the age of three years
- Single positive result for nitrite or leukocyte esterase
- Recurrent urinary tract infection
- Children who do not respond to treatment within 24-48 hours
- When clinical symptoms and dipstick tests do not correlate

Research recommendations

Further investigation of nitrite and leukocyte dipstick tests alone and in combination in an age stratified population are required to determine their accuracy in diagnosing urinary tract infection.

Further research is needed to evaluate the effectiveness of biochemical tests for low urinary glucose for diagnosing urinary tract infection in children.

Sysmex system gave a high NPV (98%) compared to dipstick tests and bacterial culture. Further evaluation of this system and the variety of selective criteria for performing the analysis is appropriate.

4.8 Laboratory investigations

A systematic review identified 10 studies assessing various clinical features for the localisation of UTI in children[132] Five additional studies were identified.[174-178]

A systematic review identified seven studies evaluated the accuracy of circulatory C-reactive protein (CRP) for diagnosing acute pyelonephritis all using DMSA as a reference standard.[132] Three studies using a concentration of 20mg/ml to define a positive result reported sensitivity above 85%, while specificity ranged from 19 to 60%. The remaining 4 studies used varying concentrations (20µg/l to 880mg/l) and reported poor diagnostic performance. For the higher concentrations sensitivity ranged from 65 to 70% and specificity

from 55% to 86%. One study with very low concentration (20µg/l) reported sensitivity of 14% and specificity of 100%.

Table 4.8.1 Summary CRP results

Positive CRP	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
>880mg/l	64	68	82	46
≥400mg/l	68	55	72	50
>200mg/l	70	57	48	77
>20mg/l	86	60	56	88
≥20mg/l	100	19	35	100
>20mg/l	95	28	49	88
>20ug/l	14	100	100	14

The systematic review reported other laboratory analytes, but the small number of studies and the diverse methodologies and cut-off points make it difficult to draw any conclusions about the value of these laboratory based tests for diagnosing UTI. [EL 1+]

An Italian study investigating markers for localising UTI and renal damage reported values for procalcitonin and C-reactive protein (CRP) at various levels.[174] Children found to have moderate to severe acute pyelonephritis were significantly more likely to have longer duration of fever (p=0.0015), higher procalcitonin level (4.48 ± 5.84ng/ml vs 0.44 ± 0.30ng/ml, p<0.0001), higher CRP level (106.0 ± 68.8mg/L vs 36.4 ± 26.0mg/L, p<0.001) (p<0.0001) and higher erythrocyte sedimentation rate (ESR) (79.1 ± 33.0mm/hour vs 58.5 ± 33.1mm/hour p=0.025) than the children with mild or no acute pyelonephritis. There were no differences between the groups in terms of age (p=0.4025), gender (p=0.781), or leukocyte count (p=0.1512) For the children with acute

pyelonephritis, the following levels of procalcitonin or CRP showed varying sensitivities, specificities and predictive values.

Table 4.8.2 Summary CRP and PCT measures[174]

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥0.8ng/ml procalcitonin	83	94	94	83
≥0.5ng/ml procalcitonin	91	70	78	87
≥1 ng/ml procalcitonin	81	94	94	81
≥20 mg/L CRP	94	32	61	83
≥50 mg/L CRP	74	77	78	72

When inflammatory markers were correlated with the severity of renal lesions (on DMSA) a significant correlation was shown with both procalcitonin and CRP levels. However, when correlated in follow-up scans, only procalcitonin remained significant.[EL II]

A study conducted in Taiwan assessed the usefulness of laboratory parameters for identifying UTI in 162 febrile infants younger than 8 weeks of age presenting to a hospital emergency department.[175]

Table 4.8.3 Summary diagnostic measures[175]

	Hemocytometer WBC counts (≥10 WBC/µl)	Standard UA (≥5 WBC/hpf)	CRP (>20 mg/L)	ESR (>30 mm/h)	Peripheral WBC (>15000/µl)
Sensitivity	82%	59%	59%	73%	36%
Specificity	94%	93%	90%	78%	80%
LR+:	12.7	8.3	5.9	3.3	1.8
LR-	0.19	0.44	0.45	0.35	0.80
ROC area	0.909 ± 0.045	0.791 ± 0.065	0.822 ± 0.036	0.787 ± 0.060	0.544 ± 0.074

There were no significant differences in the areas under the ROC curves for the standard urinalysis, CRP or ESR, however the area under the curve for hemocytmeter WBC counts was significantly better than the other laboratory parameters ($p<0.05$) and total WBC count was significantly smaller ($p<0.05$).

The most sensitive indicator to UTI was pyuria ≥10 WBC/µl (<0.05). Pyuria ≥5 WBC/hpf had poor sensitivity but high specificity. The combination of pyuria ≥10 WBC/µl and CRP>20mg/L increased the specificity to 98%, while sensitivity decreased to 54%. The specificity of pyuria ≥10 WBC/µl combined with a positive ESR increased to 97%, while the sensitivity decreased significantly to 72%. UTI was significantly more likely when the urine had ≥5 WBC/hpf or ≥10 WBC/µl.[EL II]

A study conducted in Switzerland measured procalcitonin levels in children aged 1 month to 16 years old (mean age lower UTI 36 months, mean age acute pyelonephritis 42 months)with clinical signs of acute pyelonephritis, compared to other inflammatory markers and evaluated it's ability to predict renal involvement as assessed by DMSA.[176]

There were no differences in mean age ($p=0.350$) or sex ($p=0.140$) between groups. There were significant differences between children with lower UTI and those with acute pyelonephritis in the leukocyte count (10939 ± 834 vs. 17429 ± 994, $p=0.0001$), procalcitonin level (0.38 ± 0.19 vs. 5.37 ± 1.9, $p<0.0001$) and CRP (30.3 ± 7.6 vs. 120.8 ± 8.9, $p<0.0001$). For predicting renal involvement,

CRP had a sensitivity of 100% and a specificity of 26.1%, while procalcitonin had a sensitivity of 70.3% and a specificity of 82.6%.[EL III]

One study conducted in Turkey and one study from Israel were identified investigating clinical findings compared to DMSA for localising UTI in children.[177;178] None of these studies reported raw numbers for sensitivity, specificity, PPV and NPV and were generally poor quality studies. They should be interpreted with caution.

A study conducted in Turkey evaluated 76 patients (48 girls and 28 boys) aged 2 months to 12 years to investigate whether serum levels of proinflammatory cytokines and procalcitonin in children with UTI could be used as markers in distinguishing acute pyelonephritis.[177] Significantly higher procalcitonin and proinflammatory cytokine levels were detected in children with acute pyelonephritis ($p<0.001$). Using a cut off value of 0.5ng/ml, procalcitonin showed a sensitivity of 58% and a specificity of 76%. Using a cut off value of 20mg/l, CRP showed a sensitivity of 94% and a specificity of 58%. For the inflammatory cytokines using cut off values of 6.9pg/ml, 18pg/ml and 2.2pg/ml respectively, Interleukin-1 beta (IL-ß1) showed a sensitivity of 97% and specificity 59%; Interleukin-6 (IL-6) showed a sensitivity of 88% and a specificity of 74%; and tumour necrosis factor – alpha (TNF-a) showed a sensitivity of 88% and a specificity of 80%.[EL III-]

A study conducted in Israel evaluated the ability of procalcitonin level to predict renal involvement assessed by DMSA in 64 children (44 girls and 20 boys) aged 2 weeks to 3 years (mean 16.7 ± 8.6 months).[178] CRP at a cut off value of 20mg/l showed a sensitivity of 100%, specificity 18.5%, PPV100% and NPV 30.9%. procalcitonin at a cut off value of 0.5ug/l showed a sensitivity of 94.1%, specificity 89.7%, PPV 97.6% and NPV 85.7%. [EL III-]

Evidence summary

Both CRP levels and other laboratory analytes show variable diagnostic performance in localising UTI. The small number of studies and the diverse cut-off points make it difficult to draw any conclusions about the value of these laboratory based tests for differentiating upper from lower UTI.

Procalcitonin appears to be significantly correlated with a diagnosis of UTI, however, more studies are needed to confirm this association

There is an absence of evidence upon which to draw clear conclusions about the clinical and cost-effectiveness of CRP and procalcitonin to differentiate between upper and lower tract infections.

Translation

Differentiation between upper and lower tract involvement is based on clinical findings. CRP can be utilised to help this in an appropriate clinical setting. A CRP

of < 20 may be useful in ruling out acute pyelonephritis in children with fever and in the absence of features suggestive of UTI.

CRP of <20mg/L reduces the likelihood of a serious bacterial infection. In the context of UTI, a CRP of < 20 makes the diagnosis of acute pyelonephritis unlikely.

Recommendation

CRP alone should not be used to differentiate upper from lower urinary tract infection in children.

Research recommendation

Further research is needed to evaluate the effectiveness of procalcitonin and other inflammatory markers in localising UTI.

4.9 Economic evaluation of strategies for diagnosing and managing UTI

Two economic evaluations were identified and retrieved for further assessment as part of the systematic review of economic evidence.[132;179]

One economic evaluation examined alternative strategies for the diagnosis and management of UTI and VUR in children aged two months to two years.[179] This

study found that a strategy of do nothing (observation) was the least costly strategy for diagnosing UTI while the most costly strategy was to culture urine obtained by a bag urine sample. For diagnosing VUR, the study found that a strategy of no evaluation was the least costly and a strategy of renal ultrasonography followed by VCUG was the most costly. Costs in this study are presented in USA Dollars and outcomes are not expressed in a general currency such as quality adjusted life years, limiting the study's applicability to an NHS setting.

Another economic evaluation was identified that examined the cost-effectiveness of strategies for the diagnosis and further investigation of children under with UTI.[132] The model considered 79 strategies including treat none (with no diagnostic test), treat all (with no diagnostic test) and other combinations of urine testing for UTI and imaging for identifying VUR. Outcomes were measured in decrements in quality of life experienced as a result of urine infection and the development of long term morbidities believed to be related to urine infection in childhood. Cost were reported in UK Pounds.

Significant changes in the management of UTI in children have been proposed following the systematic reviews of clinical and economic evidence in this guideline. As a result of these changes, the conclusions of the economic evaluations identified as a part of the review process are not considered appropriate within the new clinical pathway.

1

2 **Evidence summary**

3

4 There is no economic evaluation that is directly applicable to the UK setting
5 based upon appropriate assumptions for diagnosis and management of children
6 with UTI.

5 Management

5.2 Antibiotic treatment for symptomatic UTI

A variety of antibiotics are available in the UK to treat acute UTI in infants and children. The choice of antibiotics, route of administration and the duration of treatment is dependant on a combination of clinical presentation and local and individual preferences. This chapter aims to summarize the different considerations in the administration of antibiotics for the management of a first time urinary tract infection.

5.2.1 Oral antibiotic treatment

Three RCTs were identified comparing different oral antibiotic treatments for children with UTI.[180-182]

An RCT conducted in Israel randomised 94 children aged 6 months to 13 years with symptoms of urinary tract infection to oral cefixime or oral TMP/SMX.[180] Peripheral white blood cell counts, erythrocyte sedimentation rate, body temperature and urianalysis returned to normal at the same rate in both groups.[EL 1+]

The second two RCTs were graded 1- due to methodological issues and should not be used as a basis for recommendations.

An RCT conducted in the USA randomized 125 children aged 6 months to 12 years with uncomplicated UTI to receive oral TMP or oral TMP/SMX, however less than 50% of children were evaluated.[181] There were no differences in bacteriological outcome (p=0.5546) or for clinical response (equivalent) between the treatments.[EL 1-]

An RCT conducted in the USA randomized 229 children aged between 6 months and 10 years to TMP/SMX or SMX alone for three days.[182] After three days, 118 children remained in the study and were provided antibiotics for a further 7 days. A further 19 children were lost to follow-up leaving 99 children. There were no significant differences in responses to therapy at 10 days in terms of urine sterilisation, or adverse effects.[EL 1-]

5.2.2 IV antibiotic treatment

A systematic review[183] identified four RCTs comparing the effectiveness of different IV antibiotic treatments for children with acute pyelonephritis. These studies were unable to be pooled as they each investigated different IV antibiotics, so are reported individually.

The first RCT involved 20 children and compared 14 day IV cefotaxime (a third generation cephalosporin) to 7 day IV amoxicillin/clavulanic acid followed by 7 day oral amoxicillin/clavulanic acid.[184] The study numbers were small and showed no significant differences between the treatment groups for bacteriuria, recurrent infection persistent fever or gastrointestinal adverse events. Two children treated with cefotaxime had persistent bacteriuria at 48 hours. Two children treated with cefotaxime had persistent fever at 48 hours. Three children treated with amoxicillin/clavulanic had adverse gastrointestinal effects.

The second RCT involved 299 children and compared IV cefipime (a fourth generation cephalosporin) to IV ceftazidime (a third generation cephalosporin).[185] There were no significant differences between the treatment groups in the number of children with persistent bacteriuria at the end of treatment (RR 3.05, 95%CI 0.13 to 74.16); in the occurrence of an unsatisfactory clinical response at the end of treatment (RR 0.68, 95%CI 0.12 to 4.02); or in adverse events (RR 1.12, 95%CI 0.76 to 1.63) including drug-related, gastrointestinal, cutaneous or discontinuation.

The third RCT involved 100 children and compared IV cefotaxime to IV ceftriaxone in children over the age of 24 months.[186] There were no significant differences between the treatment groups for bacteriuria at the end of treatment (RR 0.87, 95%CI 0.37 to 2.03), recurrent infection at one month (RR 0.68, 95%CI 0.30 to 1.50) or for adverse events (RR 0.67, 95%CI 0.12 to 3.82) including skin

eruptions or gastrointestinal side effects. Post hoc analysis revealed no differences between children with and without abnormalities.

The fourth RCT involved 16 children and compared IV administration of the aminoglycosides isepamicin and amikacin.[187] There were no significant differences between the treatment groups for bacteriuria or resolution of fever. No child had persistent bacteriuria after 48 hours treatment and the mean time to fever resolution was identical (24 hours).

5.2.3 IV vs. oral

A systematic review[183] identified two studies comparing 10 to 14 days of oral antibiotics (cefixime or amoxicillin/clavulinic acid) with IV ceftriaxone for three days until defervescence, followed by oral antibiotics in 693 children.

Overall, there were no significant differences between the groups in the time to fever resolution (WMD 1.54, 95%CI -1.67 to 4.76), the rate of symptomatic recurrences within six months (RR 0.67, 95%CI 0.27 to 1.67) or the rate (RR 1.45, 95%CI 0.63 to 3.03) or size (RR -0.70, 95%CI -1.74 to 0.34) of renal parenchymal defects on DMSA at 6 months.[EL 1++]

5.2.4 Switch therapy

Switch therapy most often consists of intravenous therapy initially, followed by a switch to oral antibiotics as quickly as possible. The rationale behind switch therapy is considerable cost savings both to the patients and to the health care system including decreasing the complications of IV therapy and decreases the costs of administering antibiotics. Initiation of intravenous antibiotic therapy when patients are admitted to the hospital assures maximal care for those with serious infection. However, as the antibiotic takes effect and symptoms subside, usually within 72 hours, most patients are able to take oral medications.

A systematic review [183] identified four RCTs investigating short duration IV antibiotics followed by oral therapy compared to longer duration IV antibiotics.

The first RCT involved 36 children and compared IV ceftriaxone followed by oral ceftibuten 24–48 hours after defervescence (total duration 10 days) with 10 days IV ceftriaxone (the children in the first group were discharged after switching to oral antibiotics).[188] There were no significant differences between the treatment groups in persistent renal damage, recurrence, persistence of bacteriuria or adverse events.

The second RCT involved 229 children and compared 3 days' IV ceftriaxone followed by 12 days' oral cefixime with 10 days' IV ceftriaxone followed by 5 days' oral cefixime [189]. There were no significant differences between the treatment groups in persistent renal damage or recurrence.

The third RCT involved 147 children and compared 4 days' IV ceftriaxone and IV netilmicin followed by oral cefixime alone for 6 days with 4 days' IV ceftriaxone and IV netilmicin followed by IV ceftriaxone alone for 6 days [190]. There were no significant differences between the treatment groups in persistence of bacteriuria, recurrence or adverse effects.

The fourth RCT involved 87 children and compared 3 days' IV temocillin followed by 18 days' oral treatment (amoxicillin or amoxicillin plus clavulanic acid) with 7 days' IV temocillin followed by 14 days' oral treatment.[191].Both groups remained in hospital for the initial 7 days. There were no significant differences between the treatment groups in persistence of bacteriuria, recurrence or persistent renal damage. Temocillin is not licensed for use in children in the UK.[192]

Overall the systematic review found no significant difference between the treatment groups for recurrent UTI within 6 to 12 months (RR 1.15, 95%CI 0.52 to 2.51), persisting renal parenchymal defects seen on DMSA at 3–6 months (RR 0.99, 95%CI 0.72 to 1.37) or adverse effects (gastrointestinal upset) (RR 1.29, 95%CI 0.55 to 3.05).

An additional RCT [193] was identified comparing IV amikacin or gentamicin with ampicillin for 7–10 days with IV ceftrixane for 2 days followed by oral cefixime for

8 days. There was no significant difference between the groups for the rate of response clinically or microbiologically.

5.2.5 Intra-Muscular antibiotics vs. oral antibiotics

A systematic review [183] identified one RCT investigating one dose of IM antibiotic therapy and oral therapy compared to oral antibiotic therapy alone.
One additional RCT was identified [194] and investigated one dose IM amikacin compared to 10 days of oral antibiotic therapy.

A systematic review[183] identified one trial involving 69 febrile children with acute pyelonephritis and compared one dose IM ceftrixone and 10 days' oral TMP/SMX with 10 days' oral TMP/SMX alone.[195] There were no significant differences in persistence of bacteriuria at 48 hours (RR 0.77, 95%CI 0.19 to 3.20), persistence of symptoms (RR 0.82, 95%CI 0.24 to 2.81) or adverse events (RR 1.37, 95%CI 0.33 to 5.86).

An additional RCT involved 54 girls aged one to twelve years with presumed lower urinary tract infection and two positive urine cultures, compared one dose of IM amikacin versus 10 days' treatment with oral sulfisoxazole [194]. 6/23 girls receiving IM amikacin and 4/21 girls receiving oral sulphisoxazole had at least one positive urine culture within 40 days post treatment (p>0.5).[EL 1+]

5.2.6 Treatment duration

Systemically well children

A systematic review included 10 RCTs comparing short (2 to 4 days) with standard (7 to 14 days) duration of the same oral antibiotic in infants and children aged 3 months to 18 years with mild to moderate urinary tract infection.[196]

Significant bacteriuria at study completion

Overall, following standard duration (7-14 day) antibiotics, persisting bacteriuria varied from 0% to 23% (mean 14%) and recurrent UTI following treatment ranged from 5% to 50% (mean 24%). There were no significant differences in the frequency of bacteriuria at 0-10 days after completing treatment (RR 1.06, 95%CI 0.64 to 1.76)

Subgroup analysis revealed that the treatment effects of antibiotics containing sulphonamides (alone or in combination with trimethoprim) did not differ (RR 0.80, 95%CI 0.45 to 1.41) nor did other antibiotics not containing sulphonamides (RR 1.72, 95%CI 0.64 to 3.80)

Two studies included 60/159 children with abnormal imaging on IVU or MCUG. Children with abnormal imaging did not differ in their response to treatment

durations (RR 0.71, 95%CI 0.38 to 1.32) when compared to children with normal imaging (RR 0.99, 95%CI 0.12 to 8.56)

Recurrent UTI

Overall, no there significant differences in the number of UTIs at one month to fifteen months of follow up (RR 0.95, 95%CI 0.70 to 1.29). Subgroup analysis revealed that recurrence of UTI did not differ between antibiotic groups for antibiotics containing sulphonamides (RR 0.96, 95%CI 0.64 to 1.44) nor other antibiotics not containing sulphonamides (RR 0.93, 95%CI 0.53 to 1.61).

Development of resistant organisms

One study found no significant differences between short and standard duration therapy for urinary pathogens resistant to the treating antibiotic (RR 0.57, 95%CI 0.32 to 1.01)and three studies found no significant difference for recurrent UTI (RR 0.39, 95%CI0.12 to 1.29)

Systemically unwell children

A systematic review[183] identified three studies comparing different durations of antibiotic administration for children with acute pyelonephritis. Two studies use antibiotics licensed for children in the UK and compared single dose IV antibiotics (one trial IV gentamicin, one trial IV cefotaxime) with oral antibiotics given for 7 to

10 days in 61 children. There were no significant differences in persistent bacteriuria following treatment (RR 1.73, 95%CI 0.18 to 16.30) or recurrent UTI within 6 weeks (RR0.24, 95%CI 0.03 to 1.97)

5.2.7 Dosing regimens

Aminoglycosides are antibiotics that are often administered into veins or muscle to treat serious bacterial infections including UTI in children. Single daily dosing of aminoglycosides is possible because of their rapid concentration-dependent killing and post-antibiotic effect and have the potential for decreased toxicity. A systematic review[183] identified three studies investigating dosing regimens for IV aminoglycosides and one additional study was identified investigating intra-muscular aminoglyosides. All studies compared once daily dosing to three times daily in children with acute pyelonephritis.

A systematic review[183] (EL 1++) identified three studies investigating dosing regimens of IV aminoglycoside therapy in 495 children with acute pyelonephritis. Two studies investigated once daily dosing compared to eight-hourly dosing of IV gentamicin[197;198] and one study investigated IM netalimicin.[199]

Overall the systematic review found no significant difference between the treatment groups for persisting bacteriuria one to three days after commencing

treatment (RR 1.98, 95%CI 0.37 to 10.53), increase in serum creatinine during treatment (RR 0.75, 95%CI 0.20 to 2.82) or hearing impairment following treatment (RR 2.83, 95%CI 0.33 to 24.56).

The first RCT involving 172 children compared once daily IV gentamicin with IV gentamicin administered three times daily.[197] In addition to the pooled results, there were no significant differences between the treatment groups in time to defervescence (WMD 2.40, 95%CI -7.2 to 12.72) or renal parenchymal damage at three months (RR 0.66, 95%CI 0.32 to 1.36)

The second RCT involving 179 children compared IV gentamicin once a day with IV gentamicin three times a day.[198] In addition to the pooled results there were no significant differences between the treatment groups in persistent bacteriuria three days following treatment (RR 1.98, 95%CI 0.37 to 10.53) or time to defervescence (p=0.6). Mean time to defervescence was 27 hours (IQR 15 to 48 hours) with daily dosing and 33 hours (IQR 12 to 48 hours) with eight-hourly dosing.

The third RCT involving 144 children compared IM Netilmicin once a day compared with IM netilmicin three times a day.[199] In addition to the pooled results there were no significant differences between the groups in persistent bacteriuria one week after treatment (RR 2.84, 95%CI 0.12 to 68.57), reinfection one month following treatment or (RR 1.18, 95%CI 0.33 to 4.23).

Evidence summary

IV and oral antibiotics

There is not enough evidence to determine the relative efficacies of widely used oral antibiotics in children with UTI.

The limited number of studies, the small sample sizes and the different antibiotics used make it difficult to draw conclusions about the effectiveness of individual antibiotics for treating urinary tract infection in children.

IM

The available evidence indicates no difference between one or two day therapy with IM aminoglycosides or cephalosporins compared to oral antibiotics for treating children with cystitis or acute pyelonephritis.

Switch

Short duration of IV antibiotics followed by oral therapy (switch therapy) is safe and as effective as longer duration of IV antibiotics for treating severe urinary tract infection.

Treatment duration

There are no differences between short duration (2-4 days) and longer duration (7-14 days) of antibiotic treatment for children with lower tract UTI. Few studies, small sample sizes and wide confidence intervals could indicate imprecision.

Dosage

There appears to be no difference between once or three times daily dosing of IV gentamicin and IM netalmicin for treating children with urinary tract infections.

Translation

There appear to be no differences between individual antibiotics, which could be due to the limited data available. Clinicians should be guided by local policies and guidance from the local Microbiology laboratory where resistance patterns should be monitored.

Conventional treatment for children with acute UTI has been a 7-14 day course of antibiotics. The potential benefits of shorter courses of antibiotics, in children who are systemically well, include improved compliance, decreased antibiotic related side effects, diminished emergence of resistant organisms, and resource implications with particular respect to cost. In the absence of evidence demonstrating a difference in outcomes for children treated with short duration antibiotics compared with long duration antibiotics, short-duration treatment can be considered to be more effective with regards to cost and as effective with regards to clinical efficacy.

In the UK, IM injections are rarely used because of cultural reasons but have a role in circumstances where children refuse oral therapy or this is not possible.

Recommendations

These are based on initial stratification of patient groups based on severity of clinical presentation (see chapter 4).

Systemically well children with urinary tract infection

- Treat with 3 days oral antibiotics. The choice of antibiotics should be directed by locally developed multi-disciplinary guidance.
- If the child is still unwell after 24-48 hours carers should be advised to return for review.
- Systemically well children who return for review and who have not improved should be reassessed. If an alternative diagnosis is not made a urine sample should be sent for culture to identify the presence of bacteria and determine antibiotic sensitivity. Severely ill children should be referred to secondary care.

Systemically unwell children with urinary tract infection

- Consider referral to secondary care setting
- Treat with 10 to 14 days oral antibiotic treatment

If oral antibiotics are not tolerated and if the child is severely unwell 2-4 days IV antibiotic treatment followed by oral antibiotics for over 8 to 10 days to a total duration of 10 days is recommended

In infants and children who receive aminoglycoside (gentamicin or amikacin), once daily dosing is recommended.

In the rare circumstances where oral or IV treatment are not possible, IM treatment should be considered.

Children who are systemically unwell and who do not respond to oral, IV or IM antibiotics within 24 - 48 hours should have a repeat urine culture to identify the causative organism and the antibiotic sensitivity if an alternative diagnosis is not made.

5.3 Antibiotic treatment for asymptomatic bacteriuria

Four RCTs were identified comparing oral antibiotic treatments with no treatment for girls with asymptomatic bacteriuria.[200-203] Three RCTs did not report allocation concealment, or blinding and two studies did not randomise the whole sample of girls; but excluded those with renal parenchymal defects and/or reflux

found on imaging following initial screening. These biases are known to inflate treatment effects and these studies should not be taken into account when forming recommendations.

An RCT conducted in the UK randomised 63 girls identified on screening to have covert bacteriuria, to prophylactic antibiotics or no treatment.[200]

The only significant difference in the rate of bacteriuria was in the first six months where the treated group had a lower rate of persistent or recurrent infection (24% vs. 69%, $p<0.01$). This was confirmed in subgroup analysis where significantly more children in the treated group with normal radiology had a fewer number of infections than those with abnormal radiology. Bacteriuria was recurrent or persistent in 22% of treated children with normal radiology and 27% of children with abnormal radiology compared to children in the control group in whom 67% had normal radiology and 75% were abnormal.

20/29 children in the treatment group were available for radiological investigation 2 years after initial diagnosis, while 30/34 children in the control group were available.

In the control group 20/22 children with initially normal IVU showed no abnormality at the second investigation. One child had evidence of acute pyelonephritis (unilateral) and one child had grade I VUR.

4/8 children with initial acute pyelonephritis and/or VUR showed no change at the second investigation and in one child VUR had resolved. In the remaining 3 children one with anatomically minimal acute pyelonephritis had become

moderate; one developed moderate acute pyelonephritis and another reflux had become grade II.

In the treatment group 16/17 children with initially normal IVU showed no abnormality at the second investigation. One child had evidence of grade II VUR. 6/10 children with initial acute pyelonephritis and/or VUR showed no change at the second investigation and in two children VUR had resolved. In the remaining 2 children, one child's VUR had progressed from grades II to III and the child also had acute pyelonephritis in a previously normal kidney; the other child developed grade II reflux.

There were no significant differences in initial renal lengths on normal or abnormal radiology. In children with normal kidneys, renal growth in the initial 2 year period was lower in controls than in the treated group (0.67 ± 0.33 vs. 0.95 ± 0.58, $p<0.05$). Renal growth of abnormal kidneys in both controls and treated children was significantly lower than growth of normal kidneys in the treated group ($p<0.05$).[EL 1+]

An RCT conducted in the UK identified 252 girls aged 4 to 18 years with covert bacteriuria in a school screening program between 1968 and 1972.[201] 41 girls found to have renal involvement at the initial assessment were given prophylaxis, and the remaining 211 girls were randomised to receive prophylaxis (n=105) or no treatment (n=106). Girls with history of urinary tract infection were excluded.

Of the girls randomised to no treatment, 48/100 girls had spontaneously become abacteriuric within the 5 years of follow up. 5 developed acute pyelonephritis, 4

had symptoms suggesting cystitis and a further 9 were prescribed antibiotics for other urinary symptoms during the 5 year period.

Of the 105 girls who were randomised to prophylaxis, 3 developed acute pyelonephritis and 10 had symptoms suggesting cystitis.

Regression analysis showed no differences in renal growth over 5 years between the groups.[EL 1-]

An RCT conducted in Sweden identified girls aged 7 to 15 years with asymptomatic bacteriuria on a screening program and randomised then to prophylaxis (n=30) or no treatment (n=31).[202] 27/30 children in the treatment group and 30/31 children in the untreated group were followed up for three years.

In the treatment group 9/27 (33%) were given long-term prophylaxis because of repeated recurrences; 6/9 continued to have recurrences after 3 years prophylaxis. 13/27 required antibiotic treatment (short-course) for an episode of bacteriuria, and an additional 5/27 required two short courses of treatment, however there were no further recurrences in either group.

In the untreated group 9/31 (30%) became spontaneously abacteriuric and 5/31 (17%) became abacteriuric after penicillin for respiratory infection. 14/30 (47%) remained bacteriuric after three years. Growth of kidneys in these children was normal, there were no signs of scarring. One child developed grade I reflux.

There were no significant differences in the number of bacteriuric children in the treatment group (6/27) compared to the untreated group (14/30) at the end of the observation period.[EL 1-]

From a screening program in the UK involving 16800 girls aged 4 to 12 years, 248 with bacteriuria were randomised to receive antibiotic treatment (127) or no treatment (121).[203] During follow-up 9/110 (8%) girls in the treatment group and 8/98 (8%) in the untreated group had an infection accompanied by frequency, dysuria or loin pain and fever and were given antibiotics.

At follow up MCUG (four years later) 17/110 (15%) of the girls in the treated group had bacteriuria compared to 44/98 (45%) of girls in the control group. ($p<0.001$). No new scars were seen in girls who had normal kidneys at the initial x-ray examination. There were no significant differences in new scars in girls with scars at the initial x-ray; new and/or deepening scars were found in 12/44 (27%); 6/28 (21%) in the girls who received treatment and 6/16 (38%) in the girls who received no treatment.[EL 1-]

Evidence summary

Although the quality of three of the RCTs means they are unable to be used in recommendations, the results of all four studies are similar. There were no significant differences in persistent bacteriuria, renal parenchymal defects or renal growth between girls with asymptomatic bacteriuria irrespective of antibiotic treatment.

Recommendation

Asymptomatic bacteriuria in children should not be treated with antibiotics.

5.4 Symptomatic treatment

5.4.1 Cranberry

A systematic review[204] did not identify any studies evaluating cranberry products in any age group for treating UTI. No further studies were identified investigating cranberry juice or cranberry products for treating first time UTI in infants or children.

5.4.2 Other symptomatic treatment

No studies were identified that investigated other symptomatic treatment as a monotherapy or in addition to antibiotics in infants or children with UTI.

5.5 Recurrence

Recurrent UTI is associated with morbidity and all opportunities to prevent it should be explored. Children and carers who have experienced the debilitating

and painful effects of UTI will welcome strategies that can identify predictors and prevent recurrence. Whilst there is still much to be discovered as to the long-term effects of UTI, there is no question that individual infections are unpleasant, and often result in time missed from school, which with recurrence can have an incremental effect on learning. In this section we have attempted to define predictive factors for recurrent UTI and explore strategies excluding antibiotics that prevent recurrence.

There is wide variation in practice with regards to policies and implementation of strategies to prevent recurrent UTIs. This is more likely because of variations in the care systems and the people delivering them. However it is important to note that current strategies incorporate behaviour modification advice and do not depend on costly interventions to help achieve their end.

5.5.1 Factors predicting recurrence

Eight studies were identified which investigated factors predicting future UTIs in children who had a previous UTI. [61;205-212]

An American cohort study evaluated the relationship between early UTI, VUR and dysfunctional elimination syndrome.[205] 123 questionnaires were completed (73% response rate) for children in the UTI cohort aged 4.3 to 10 years who had a first time UTI under the age of 2 years and 125 questionnaires were completed (31% response rate) in the comparison cohort of children who were investigated

for fever and who had a negative urine culture during the same period. The groups were similar with respect to demographic and clinical characteristics. The prevalence of dysfunctional elimination syndrome did not differ between children with UTI and children without (22% vs. 21%, p=0.82). In children with UTI, the prevalence of dysfunctional elimination syndrome did not differ in children with or without VUR (18% vs. 25%, p=0.52). Further analysis using different cut-off values did not yield different results.

31 children had recurrent UTI. Of these 13 (43%) had encopresis (OR 2.5, 95%CI 1.1 to 5.4, p=0.03), 11 (36%) had dysfunctional elimination syndrome (OR 2.2, 95%CI 0.99 to 5, p=0.05) and 17 (55%) had VUR (OR 2.2, 95%CI 0.9 to 5, p=0.07). The only variable that remained significant with recurrent UTI was encopresis (p=0.03).[EL 2+]

An Australian cohort study evaluated the risk factors that predispose to recurrent UTI in children aged ≤5 yrs, presenting at a children's hospital with symptomatic UTI and the role of recurrent UTI in renal scarring.[61] At one year, 261 (90%) children were evaluated (133 girls and 157 boys). There were 46 recurrent UTIs in 34 children during 12 months of follow up; 20 children had 1 recurrence; 14 had two or more recurrences. At the initial UTI, VUR was found in 83/290 (29%) of children and renal parenchymal defects in 113/290 (39%).

In multivariable analysis, recurrence was not associated with gender (p=0.08), fever (p=0.59), VUR (p=0.5), Intrarenal VUR (p=0.54), bilateral VUR (0.6) or abnormal initial DMSA (p=0.32). Age less than 6 months at the time of first UTI

(OR 2.9, 95%CI 1.4 to 6.2, p<0.01) and dilating VUR (OR 3.6, 95%CI 1.5 to 8.3, p<0.001) were significant predictors for recurrence.

VUR

VUR was present in 14/34 (41%) with recurrent infection and 65/256 (27%) without recurrent infection. Comparison between groups showed that the presence of reflux was not associated with recurrent infection (p<0.05) but the grade of reflux (X^2=12.1, p<0.01), bilateral reflux (X^2=6.1, p<0.05) and intrarenal reflux (X^2=5.2, p<0.05) were significantly associated with recurrence. High grade reflux (grades 3 to 5) was an independent predictor of recurrence (OR 3.6, 95%CI 1.5 to 8.3, p<0.001)

Renal parenchymal defects

Repeat DMSA was performed in 173 children at 1 year. Recurrent UTI was significantly associated with renal parenchymal defects seen on first UTI (X^2=4.6, p<0.05) and there was a significant linear trend in the proportion of children with recurrent UTI with increasing grade of DMSA abnormality on entry (X^2 trend =9.6, 1df, p<0.01). Recurrent UTI was also significantly associated with DMSA abnormalities at one year (X^2=11.5, p<0.001) and recurrent febrile UTI was significantly associated with DMSA abnormalities at one year (X^2=10.1, p<0.001).[EL 2++]

A case-control study (90 cases, 45 controls) conducted in Switzerland evaluated the role of family history, infrequent voiding, poor fluid intake, functional stool retention and inadequate anogenital hygiene or toilet habits in girls with 3 or

more recurrent UTIs.[206] Of the 90 cases, sixty girls had a history of lower UTI and the remaining 30 had history of mixed UTI, upper in 16 and both upper and lower in 14.

Family history of UTI (42% of cases v 11% of controls, p<0.001), behavioural abnormalities (81% v 56%, p<0.01), infrequent voiding (54% v 24%, p<0.001), poor fluid intake (53% v 16%, p<0.001) and functional stool retention (30% v 13%, p<0.05) were more frequent in girls with recurrent infection than in controls. There were no significant differences between cases and controls for anogenital hygiene or toilet habits.[EL 2+]

A cross sectional conducted in Turkey surveyed the incidence of idiopathic hypercalciuria in 75 children (62 girls and 13 boys) with recurrent UTI.[213] Hypercalciuria was found in 32 children (43%) of whom 23 (72%) were girls and 9 (28%) were boys. Hypercalciuric children were younger (7.2 ± 2.1 vs 8.7 ± 2.9, p=0.013) and had a higher mean calcium/creatinine ratio (0.50 ± 0.21 vs 0.10 ± 0.04, p=0.01) than children with normocalciuric children. There were no significant differences between groups for voiding dysfunction, pain, haematuria, urolithiasis, family history of urolithiasis or predisposing urinary tract abnormality.[EL 3]

A cross sectional study from the USA evaluated the rate of and potential risk factors for recurrent UTI in children younger than 6 months with UTI and no abnormality on radiographic evaluation.[208] Follow up data was available for 84

(52 girls and 32 boys) and the mean follow up period was 4.4 years (range 1.9 to 7.0 years). 16/84 (19%) had at least one febrile UTI after the negative radiographic evaluation. There were no statistically significant risk factors for recurrent UTI; breast-feeding (less than 4 months) (p=0.077); siblings younger than 14 years (p=0.680); family history of UTI (p=0.325); potty training (less than 2 years) (p=0.640); neurological problems (p=0.687); undiagnosed fevers (p=0.082); constipation history (p=0.714); residence (live in private house) (p=0.598); income less than $50,000 (p=0.344); circumcision (p=0.841) [EL 3]

A cross-sectional study conducted in Belgium investigated the possible relationship between recurrent UTI and methods of potty training by comparing the methods used in children with and without recurrent UTI.[209] 4332 questionnaires were completed in children attending the last two years of primary school and were stratified into three groups; Children with a single UTI 382 (9%); Children with recurrent UTI 132 (3%); and children with no history of UTI 3818 (88%). Overall, girls were more likely to have a UTI than boys (p<0.001) and in children with recurrent UTI, more boys (51%) than girls (21%) had their first UTI in the first 2.5 years of life (p<0.001).

In children with daytime wetting, 12% had recurrent infection, compared to 2% of children with recurrent infection in children without wetting (p<0.001).

Children with recurrent UTI were more likely to have faecal soiling (9.1%) compared to children with no UTI (2.5%); nocturia at least once a week (10% vs.

3%, p<0.001); and not to have started potty training by 18 months (21% vs. 31%, p<0.05).

When an attempt to void was unsuccessful the reaction of parents/carers of children with recurrent UTI compared to children with no UTI was to keep the child on the potty until a void was obtained (11% vs. 3%, p<0.005); push or strain (13% vs. 7%, p<0.001); or turn on the tap (32% vs. 22%, p<0.001)[EL 3]

A case-series from Switzerland evaluated the role of family history, infrequent voiding, poor fluid intake, functional stool retention and inadequate hygiene or toilet habits in girls aged 3.9 to 18 years (median 6.5 years) referred to a nephrology clinic for evaluation of three or more symptomatic UTIs.[210] 88% had history of lower tract infection. 212 behavioural and functional abnormalities were found in 121 girls and no abnormalities were found in 20/141 (14%) of girls with recurrent UTI. Infrequent voiding was found in 63 (45%), poor fluid intake in 60 (43%), functional stool retention in 30 (21%), inadequate genital hygiene in 27 (19%), dysfunctional voiding in 25 (18%) and bladder over-activity in 7 (5%).

Two, three or four concomitant abnormalities were found in 66 girls. Girls without abnormalities were significantly younger than girls with abnormalities (p<0.05). Girls with dysfunctional voiding (n=25) were significantly older than other girls with abnormalities (p<0.02) [EL 3]

Baseline data from a case-control study conducted in Turkey evaluated 30 children with renal scarring and 67 children without renal scarring.[211] Children

with renal scarring were more likely to have recurrent UTIs than children without scarring (6.90 ± 2.45 UTI episodes vs. 3.35 ± 1.48 UTI episodes, p<0.001)[EL 3]

A matched cohort study conducted in the USA investigated the relationship between pinworm infestation and recurrent UTI in girls, however due to methodological limitations should not be used to base recommendations.[212] 41 girls (mean age 5.5 years) referred for evaluation of the urinary tract were compared to 58 girls (mean age 6.4 years) who had no history of urinary, vaginal or pinworm infection. 9/41 (22%) of girls with recurrent UTI had a positive scotch tape test compared to 3/58 (5%) of controls and 31/41 (75%) of girls with recurrent UTI had a positive introital enterics culture compared to 25/58 (43%) of controls.[EL 2-]

Evidence summary

Age less than 6 months at the time of the first UTI, family history of UTI, dilating reflux, infrequent voiding, poor fluid intake and functional stool retention may be associated with an increased risk of recurrent UTI in children, however evidence is limited.

Infrequent voiding, poor fluid intake, functional stool retention, inadequate genital hygiene, dysfunctional voiding and bladder over-activity may coexist to varying degrees.

Table 5.5.1.1 Summary factors predicting recurrence

Reference	[205]	[61]	[206]	[208]	[209]	[211]
	N=123	N=261	N=90 cases, 45 controls	N=84	N=4322	N=30
Gender		(p=0.08)				
Breast-feeding	-	-	-	P=0.077	-	-
Age under 2.5		p<0.01				
Family history of UTI	-	-	<0.001	0.325	-	-
Constipation	-	-	-	0.714	-	-
Circumcision	-	-	-	0.841	-	-
Dysfunctional voiding*	0.05	-	<0.001	-	p<0.001	-
Poor fluid intake	-		<0.001	-	-	-
Functional stool retention/encopresis	0.03	-	P<0.05	-	-	-
Inadequate toilet habits	-	-	NS	-	-	-
Reflux	0.07	p=0.5	-	-	-	-
Renal scarring (on initial DMSA)	-	p<0.05			-	p<0.001

*includes infrequent voiding, nocturia

5.5.2 Non-antibiotic strategies for preventing recurrence

No studies were identified which investigated strategies other than antibiotics for preventing recurrence in infants and children with UTI. Studies were identified about predisposing factors for first time UTI (see section 4.2) and for recurrent UTI (see section 5.5.1). Consensus recommendations based on these reviews were made.

Translation

There is little evidence supporting strategies that could be of value in preventing recurrent UTI. However experience, combined with this weak evidence, indicates that a thorough assessment of a child's voiding history, bowel management and hygiene can highlight areas which can be addressed and be effective in the prevention of further infection. Dysfunctional voiding includes many aspects of bladder miss-management, including a learned ability to delay voiding, resulting in poor emptying and high volume residuals. This could be addressed by improving opportunities, providing adequate toilet facilities and the environment to assist adequate and timely bladder emptying. A holistic approach incorporating strategies that address all these issues would facilitate the best management for the children and help their carers in delivering it.

Although there is very little evidence from paediatric studies, cranberry juice has been shown to prevent recurrent UTI in adult patients in different circumstances. This data could be extrapolated into strategies for preventing UTI in children, however the GDG were unable to make a recommendation. However it should be noted that this should be avoided by patients who are on anticoagulant therapy.

There is no evidence to suggest that reducing caffeinated and high sugar drinks will prevent UTI, these are not considered advisable as part of healthy dietary intake.

There is evidence to relate VUR and recurrence.

Recommendations

Dysfunctional elimination syndromes and constipation should be addressed in children who have had a UTI.

Children who have had a UTI should be encouraged to drink an adequate amount.

Parents and carers should be advised to prevent children from delaying voiding by ensuring ready access to clean toilets when required at all times.

5.5.3 Antibiotic prophylaxis

Repeated episodes of acute urinary tract infection can be distressing to children, young people and their parents or carers. Antibiotic prophylaxis aims to reduce the risk of recurrent, symptomatic urinary tract infections. A systematic review[214]identified eight studies comparing antibiotic treatment with placebo or no treatment for preventing recurrent UTIs in children. Of the six studies with appropriately reported data the participants were mostly females aged between 6 months and fourteen years. [EL 1++]

An additional systematic review[215] investigated interventions for primary VUR and identified one RCT; and two further RCTs were identified.[60;216]

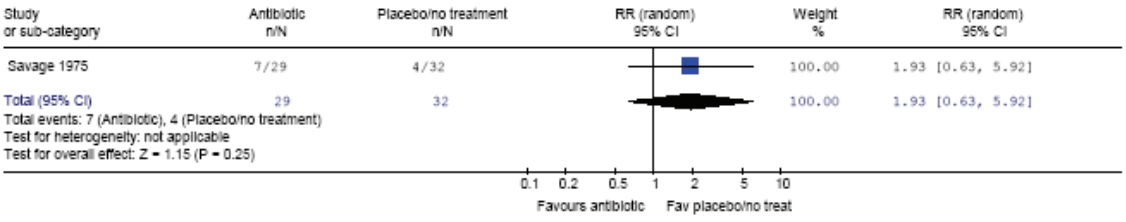
A systematic review[214]identified six evaluable studies comparing antibiotic treatment with placebo or no treatment for preventing recurrent UTIs in children. Four studies compared antibiotics with placebo or no treatment in children with

previous frequent recurrent UTI with normal renal tracts. One study compared effectiveness of nitrofurantoin with trimethoiprim over a six month period and another study compared the effectiveness of cefixime with nitrofurantoin during either a six or twelve month period. The primary outcome was the number of repeat symptomatic UTIs confirmed by bacterial growth in the urine. Recurrent UTIs were defined as subsequent UTIs caused by different bacteria to the initial infection. Secondary outcomes included total number of symptomatic UTIs, adverse events, hospitalisation with UTI and febrile UTI. . The trials included in this review were small and poorly designed with biases known to overestimate the true treatment effect.

Antibiotic vs. placebo for prevention of recurrence of symptomatic UTI

One study evaluated this outcome. Compared to the placebo group there were almost, twice as many recurrent symptomatic UTIs in the group treated with antibiotics (RR 1.93, 95%CI 0.63 to 5.92, p=0.25).

Table 5.5.3.1 Antibiotic treatment vs. placebo, outcome recurrent symptomatic UTI

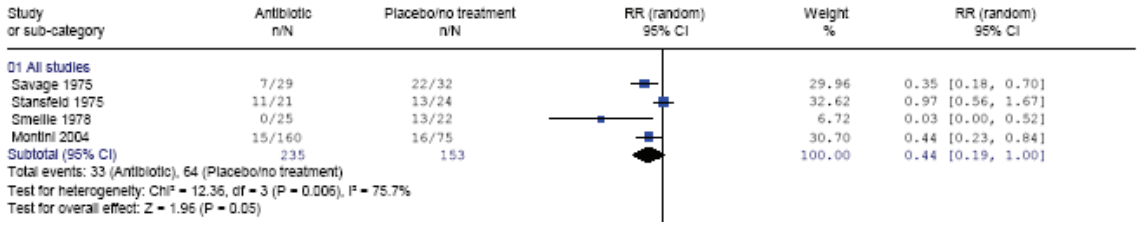


Antibiotic vs. placebo for prevention of repeat positive urine culture

Four studies evaluated this outcome. Overall, antibiotics reduced the risk of repeat positive urine culture (RR 0.44, 95%CI 0.19 to 1.0, p=0.06). In the two studies with adequate concealment antibiotics reduced the risk of repeat positive urine culture (RR 0.66, 95%CI 0.3 to 1.39) and in one study which was double blinded antibiotics showed (RR 0.97, 95%CI 0.56 to 1.67).

There were no reported antibiotic side effects or hospitalisation with repeat positive urine culture. The treatment effect was inflated in studies which were not of high quality.

Table 5.5.3.2 Antibiotic treatment vs. placebo, outcome repeat positive urine culture



Antibiotic vs. placebo, the presence of VUR and risk of repeat positive urine culture.

Two studies reported the results of repeat positive urine culture for children with VUR and for children without VUR. Compared to placebo antibiotics reduced the risk of repeat positive urine culture in children without VUR

(RR 0.14, 95%CI 0.01 to 1.76; RD -54%, 95%CI -70% to -37%). In children with VUR the RD was -60% (95%CI -104% to -16%) however there was considerable heterogeneity between studies.

Antibiotic duration

There were no consistent trends in treatment effect for antibiotic duration. Data was limited; one study reported 10 weeks duration, one study reported 6 months and two reported 12 months.

Antibiotic effectiveness

One study compared the effectiveness of nitrofurantoin with trimethoprim over a 6 month period. Nitrofurantoin was more effective in preventing recurrent UTI than trimethoprim (RR 0.48, 95%CI 0.25 to 0.92; RD -18%, 95%CI -34% to -3%). However, patients receiving nitrofurantoin were three times more likely to discontinue the antibiotic due to side effects (nausea, vomiting or stomach ache) than patients receiving trimethoprim (RR 3.17, 95%CI 1.36 to 7.37; RD 22%, 95%CI 8% to 36%). Side effects of nitrofurantoin may outweigh its prophylactic effects (NNH = 5, 95%CI 3 to 13) compared with trimethoprim (NNT = 5, 95%CI 3 to 33).

One study compared nitrofurantoin with cefixime. There were no significant differences between treatments (RR 1.35, 95%CI 0.24 to 7.48)

An additional systematic review[215] identified one RCT which randomised children with vesicoureteric reflux to receive no treatment, daily antibiotic prophylaxis or prophylaxis given three days a week. There were no significant differences between daily antibiotic prophylaxis and no prophylaxis (RR 0.25, 95%CI 0.03 to

1.83) or between three day a week prophylaxis and no prophylaxis (RR 0.46 95%CI 0.10 to 2.00)

There were no differences in the risk of renal parenchymal damage between daily antibiotic prophylaxis and no prophylaxis (RR 0.40 95%CI 0.02 to 9.18) or between three day a week prophylaxis and no prophylaxis (RR 0.38 95%CI 0.02 to 8.59).

An RCT conducted in the United States recruited children who had an episode of acute pyelonephritis and randomised those who had VUR and those who did not have VUR to antibiotic prophylaxis or no prophylaxis.[60]

Rates of spontaneous resolution of VUR did not differ between groups; after one year resolution rates were 37.5% (grade I), 12.5% (grade II) and 10.3% (grade III).

Of the children not receiving prophylaxis 22.4% with VUR had a recurrence compared to 23.3% of children who did not have VUR (p=0.9). Recurrent acute pyelonephritis was observed in 7 children compared to only one of the children who did not receive prophylaxis (p=0.0291), however in all 7 cases the bacteria showed resistance to the antibiotic used.

Of the children receiving prophylaxis, 23.6% with VUR had a recurrence compared to 8.8% of children who did not have VUR (p=0.063).

13/218 children developed renal scars during the one year follow up period. There were no differences between those with VUR and those without, nor between those receiving prophylaxis compared to no prophylaxis.[EL 1+]

An RCT conducted in Australia evaluated the effectiveness of low-dose, long-term antibiotics to prevent UTI and renal damage in 46 children.[216] 29/46 had grades III to V (12 in the prophylaxis group and 18 in the placebo group) and 17 had reflux less than grade III. 5 children were lost to follow up (3 placebo, 2 antibiotic)

2 children in the placebo group and no children in the prophylaxis group developed a UTI (p=0.2). No child in either group developed renal scarring on DMSA. Renal growth (2.42 cm vs. 2.83 cm p=0.8) and GFR (119 vs. 108mls/min/1.73m2, p=0.3) were no different between the groups.

Assuming absolute risk reduction of 30% over three years with long-term antibiotics, 2000 foetuses would need to be screened to detect 20 with renal tract dilatation of whom 3 would have VUR. With treatment over three years with daily antibiotics, 1 episode of UTI would be prevented.[EL 1+]

Evidence summary

The small number of poor quality studies available do not provide clear evidence to assess the effectiveness of antibiotic prophylaxis in preventing recurrent UTI, in particular, only one study evaluated prophylactic antibiotics for reducing symptomatic UTI.

Nitrofurantoin may be more effective than trimethoprim, however the side effects may outweigh its prophylactic effectiveness.

Translation

Whilst prophylaxis has been commonly used in recurrent UTI, it has no apparent effect in reducing the number of infections, it will however reduce the number of repeat positive urine cultures. It cannot be considered to be a useful strategy for the prevention of further kidney scarring both in terms of clinical and cost effectiveness.

Recommendations

Antibiotic prophylaxis should not be routinely recommended in children with urinary tract infection.

Research recommendations

Well designed randomized, double blinded, placebo controlled trials are required to determine the effectiveness of prophylactic antibiotics for preventing subsequent symptomatic UTIs and renal parenchymal defects in children.

6 Imaging

6.1 Introduction

Once a urinary tract infection in a child has been confirmed by urine testing, current practice is to request one or more imaging investigations to look for urinary tract abnormalities that may have predisposed the child to infection or for complications of the infection.

The most recent guidance on the use of imaging following urinary tract infection in childhood was published by the Royal College of Physicians in 1991[26] This states that infants should undergo ultrasonography of the urinary tract, a micturating cystourethrogram (MCUG) and renal scintigraphy (Tc99m labelled dimercaptosuccinic acid - DMSA). Additionally, the guidance stated that children between one and seven years of age should have an ultrasound scan and a DMSA scan, and those over the age of seven years, should have an ultrasound scan with further imaging being directed by the results of this scan.

This guidance was a consensus document which accepted the assumption that infection associated with reflux was responsible for renal parenchymal defects. The implication was that by managing those thought to be at risk of developing renal parenchymal defects (those with reflux) and those who had proven defects

with prophylactic antibiotics, further defects and progression to end stage renal failure could be prevented.

However it has proved difficult to estimate accurately the risk of urinary tract infection in childhood leading to end stage renal failure (see chapter 3.4). Furthermore the value of long term antibiotic prophylaxis and the low yield of abnormalities (renal parenchymal defects) on imaging has prompted a reassessment of the risks and benefits of intensively imaging all children with urinary tract infection. Clinicians have questioned whether it would be better to target imaging investigations at those children who are perceived to be at greater risk, and not image every child who has an otherwise uncomplicated urinary tract infection.

Current imaging strategies following UTI in childhood are based on evaluating renal structure and the presence of dilatation (ultrasound), the detection of vesico-ureteric reflux (MCUG) and of renal parenchymal defects (DMSA). Very occasionally imaging is used acutely to localise infection to the renal parenchyma (DMSA), though in practice this is usually a clinically based assessment.

Whilst there is reasonable evidence about the accuracy of individual imaging investigations in the detection of specific abnormalities (eg. vesico-ureteric reflux, renal parenchymal defects, hydronephrosis), there is no high quality evidence about any benefit from imaging in the majority of children who have had a UTI.

Evaluation of the structure of the urinary tract

Ultrasound is currently the first line imaging investigation in children who have had a urinary tract infection. This is a widely available technique which uses high frequency sound to image the urinary tract. It does not use ionising radiation and is non invasive, making it ideally suited for children.

Ultrasound can rapidly assess renal size, the presence of collecting system or ureteric dilatation and evaluate the bladder (including bladder emptying). It can be used to indicate obstruction, congenital abnormalities of the urinary tract and calculi, that may require specific management.

The use of power doppler permits some functional information about the renal blood supply and regional perfusion and may provide information about renal parenchymal involvement by infection.

Other imaging techniques which can provide anatomic detail of the urinary tract are MCUG, IVU and MRI. Only MCUG is used routinely in the evaluation of children with urinary tract infection – further details of IVU and MRI can be found in the glossary,

Detecting VUR

Vesicoureteric reflux (VUR) occurs when urine passes retrogradely from the bladder into one or both ureters and often to the kidneys. Much of the imaging of children following urinary tract infection has been focussed on the detection of VUR because of the association described between urinary tract infection, VUR and the development of renal parenchymal defects (scars). The incidence of VUR is known to be higher in children investigated after urinary tract infection (30-40%) (see chapter 3.3) than in the normal population (1-3%).

There are several imaging techniques available to detect VUR including the micturating cystourethrogram (MCUG), the direct and indirect radionuclide cystogram and cystosonography. All have advantages and disadvantages. MCUG is considered the 'gold standard' for the detection of VUR. The Royal College of Physicians guidelines[26] recommended that it should be performed in all infants who have had a urinary tract infection. This is the only imaging modality which can reliably provide information about the urethra.

An alternative technique in older children who are toilet trained is an indirect radionuclide cystogram, performed as an adjunct to a MAG3 examination.

However there is a radiation penalty with MCUG (1mSv) which is equivalent to about 4 months of natural background radiation, though the introduction of dose

reduction techniques can minimise this. Complications of MCUG include urethral trauma and the introduction of infection into the urinary tract. Most children and their parents/carers find this investigation distressing.[31] A full description of MCUG and other techniques to image reflux can be found in the glossary.

Renal parenchymal defects

The detection of renal parenchymal defects has historically been important in children following urinary tract infection. Renal parenchymal defects encompass acquired scarring as well as congenital dysplasia. Not all renal parenchymal defects detected by imaging represent foci of acquired parenchymal destruction, and any one imaging test cannot determine whether a defect is congenital or acquired (ie. a scar).

The presence of acquired parenchymal defects has been considered a risk factor for the development of hypertension and end-stage renal failure. Approximately 5% of children who have had a urinary tract infection will have evidence of at least one renal parenchymal defect, while a much higher proportion of children (approximately 40%) with VUR are likely to have renal parenchymal defects. Acquired lesions and/or dysplasia are not always seen as focal defects but may appear as a global reduction in size with commensurate decreased function of the affected kidney.

In the UK, current practice is to perform a DMSA scan 6 months after the urinary tract infection. Scans performed earlier are more likely to show transient defects due to inflammation which may be misdiagnosed as a permanent renal parenchymal defect. The Royal College of Physicians recommended antibiotic prophylaxis for all children under 7 until the completion of imaging tests; although the majority of children will have no renal parenchymal defects.

Other imaging techniques including ultrasound, MRI and MAG3 renography are able to identify renal parenchymal defects. For a description of DMSA and these other techniques, please refer to the glossary.

Localisation of infection

It may very occasionally be important to attempt to differentiate infection confined to the lower urinary tract (urinary bladder) from upper tract infection (renal parenchyma – acute pyelonephritis) by imaging to guide management. Ultrasound may give some indication of renal parenchymal involvement but DMSA is considered to be the gold standard.

The following section comprises a comprehensive evaluation of the accuracy of the various imaging tests available to assess the urinary tract following UTI in children. It is based almost completely on a Health Technology Appraisal[132] which looked solely at technical (and not clinical) utility of these tests. Much of what follows in the next sections is taken directly from the HTA.

There is limited evidence available to evaluate the role of these tests in influencing outcomes of children following urinary tract infection, and to base recommendations on.

6.2 Evaluation of the structure of the urinary tract

No high quality studies were identified investigating tests for assessing structural abnormalities in children with UTI. Ultrasound is the reference standard for diagnosing abnormalities.

Translation

Imaging studies were recommended to identify children at greatest risk of renal damage and recurrent UTI. It is clear that the incidence of abnormalities such as obstruction that affect management is very low in children after 6 months of age and in children presenting with mild or moderately severe illness.

The relatively low prevalence of significant anatomic abnormalities in children with uncomplicated UTI suggests that routine imaging is unnecessary. Imaging to

look for obstruction or other abnormalities that may need specific management should be reserved for those children who are ill or do not respond promptly to treatment.

The prevalence of VUR and renal scarring is well known but there is no evidence that the interventions proposed such as prophylaxis and surgery influence the outcome, except in children with recurrent acute pyelonephritis. In these children there is a reduction of recurrent upper tract infection following re-implantation of the ureter.

Recommendations

In all children with severe or atypical illness who do not respond to treatment within 48 hours, early ultrasound scan is recommended to identify structural abnormalities of the urinary tract. (Table 6.7.1 – 6.7.3)

In infants aged 0 to 6 months, late ultrasound (within 6 weeks) should be carried out following the first simple urinary tract infection. (Table 6.7.1 – 6.7.3)

In children over 6 months of age with simple first time UTI that responds to treatment, routine ultrasound is not recommended. (Table 6.7.1 – 6.7.3)

6.3 Vesicoureteric reflux

Forty studies were identified. Of these, a systematic review identified 34 studies reporting 57 data sets investigating tests for the detection of reflux[132] and a further six studies were identified.[217-222] The reference standard for detecting VUR is MCUG.

6.3.1 Ultrasound

Conventional Ultrasound

A systematic review identified 11 studies evaluating the use of ultrasound for detecting reflux compared with the reference standard of MCUG.[132]

Sensitivity ranged from 10.5% (specificity 89.4%) to 90.9% (specificity 14.6%) and specificity from 14.6% (sensitivity 90.9%) to 93.8% (sensitivity 53.7%).

Likelihood ratios showed significant heterogeneity ($p<0.0001$). Positive likelihood ratios ranged from 1.0 (LR- ~ 1.0) to 8.7 (LR- = 0.49) and negative likelihood ratios ranged from 0.41 (LR+ = 8.2) to 0.98 (LR+ ~ 1.0). The pooled positive likelihood ratio was 1.9 (95%CI 11.2, 2.9) and the pooled negative likelihood ratio was 0.76 (95%CI 0.63, 0.93).

The median positive likelihood ratio was 1.4 (IQR 1.1 to 2.5) and the median negative likelihood ratio was 1.4 (IQR 0.58 to 0.98).

Calculated predictive values of conventional ultrasound for detecting reflux for PPV ranged from 15% to 90% and for NPV ranged from 56% to 99%.

Table 6.3.1.1 Standard ultrasound vs. MCUG[1]

Study details	Test details; time	Definition of positive result	Reference standard; definition of positive result	Unit of analysis	Sens	Spec	LR+	LR-
Standard ultrasound vs. MCUG								
Baronciani 1986	Standard	Presence of reflux; dilation or hydronephrosis	MCUG; presence of reflux	Patients	61.9	92.5	8.2	0.41
Evans 1999	Standard	Presence of reflux (change in pelvic diameter)	MCUG; presence of reflux	Renal units	10.5	89.4	1.0	1.0
Foresman 2001	Duplex	Any abnormality	MCUG; presence of reflux	Patients	49.0	52.2	1.0	0.98
Mage 1989	Standard	Not stated	MCUG; presence of reflux	Patients	53.7	93.8	8.7	0.49
Mahant 2002	Standard	Presence of reflux (dilation	MCUG; presence of reflux	Patients	40.0	76.4	1.7	0.79
Morin 1999	Standard	Renal changed indicative of APN	MCUG; presence of reflux	Patients	90.9	14.6	1.1	0.62
Muensterer 2002	Standard	Abnormal kidney size or dilation	MCUG; presence of reflux ≥ grade 3	Renal units	91.3	67.5	2.8	0.15
		Presence of reflux (dilation)	MCUG; presence of reflux	Renal units	50.7	76.0	2.1	0.65
		Abnormal kidney size	MCUG; presence of reflux	Renal units	29.0	91.2	3.3	0.78
		Abnormal kidney size	MCUG; presence of reflux ≥ grade 3	Renal units	47.8	89.8	4.7	0.58
		Presence of reflux (dilation)	MCUG; presence of reflux ≥ grade 3	Renal units	78.3	74.7	3.0	0.31
Oostenbrink (2000)	Standard	Presence of reflux (at least mild dilatation)	MCUG; presence of reflux	Patients	56.8	80.6	2.9	0.54
Salih 1994	Colour Doppler	Presence of reflux (blue-coloured jet)	MCUG; presence of reflux	Renal units	96.3	80.0	4.8	0.05
Tan 1988	Standard	Not stated	MCUG; presence of reflux	Patients	17.6	84.2	1.1	0.98
Trave 1997	Standard	Not stated	MCUG; presence of reflux	Renal units	17.6	87.1	1.4	0.95
Verber 1988	Standard	Presence of reflux or scarring	MCUG (Hypaqure); presence of reflux	Renal units	28.6	73.5	1.1	0.97

[1] Taken from the Health Technology Assessment 'Clinical and Cost Effectiveness of tests for the diagnosis of urinary tract infection in children: a systematic review and economic model

An Israeli study compared renal ultrasound with MCUG for detecting VUR in a population of 252 children under the age of 5.[218] The sensitivity, specificity, positive and negative predictive vales for ultrasound were 16%, 88%, 24%, and 83%, respectively.[EL II]

Contrast enhanced ultrasound (cystosonography)

A systematic review identified 14 studies evaluating the diagnostic accuracy of cystosonography for detecting reflux using MCUG as the reference standard.[132] None of the studies included an appropriate spectrum of patients, some had a UTI, some did not have a UTI. 8 studies did not include sufficient detail of the reference standard to allow replication and 6 did not report sufficient information to assess review bias, where interpretation of the results of the index tests may be influenced by the knowledge of the results of the reference standard or vice versa.

Sensitivity ranged from 56.8% (specificity 84.8%) to 96.3% (specificity 80%). In all but three studies sensitivity was above 75%. Specificity ranged from 80% (sensitivity 96.3%) to 100% (sensitivity 76.5% and 85.7%).

Likelihood ratios showed significant heterogeneity (p<0.0001). Positive likelihood ratios ranged from 3.8 (LR- = 0.51) to 71.2 (LR- = 0.20) and negative likelihood ratios ranged from 0.04 (LR+ = 25.6) to 0.51 (LR+ = 3.8). The pooled positive likelihood ratio was 12.3 (95%CI 8.2, 18.3) and the pooled negative likelihood ratio was 0.17 (95%CI 0.11, 0.27).

The median positive likelihood ratio was 13.7 (interquartile range 9.1 to 30.8) and the median negative likelihood ratio was 0.16 (interquartile range 0.11 to 0.23).

Calculated predictive values of contrast enhanced ultrasound for detecting reflux for PPV ranged from 55% to 100% and for NPV ranged from 86% to 100%.

1 **Table 6.3.1.2 Contrast enhanced ultrasound vs. MCUG[2]**

2

Study details	Test details; time	Definition of positive result	Reference standard; definition of positive result	Unit of analysis	Sens	Spec	LR+	LR-
Alzen 1994	Air contrast	Not stated	MCUG; presence of reflux	Renal units	90.9	92.4	12.0	0.10
Bergius 1989	Cystosonography (Isopaque)	Presence of reflux ≥ grade 3 (air bubbles)	MCUG; presence of reflux ≥ grade 3	Renal units	90.5	99.6	134.7	0.11
		Presence of reflux ≥ grade 2 or air bubbles	MCUG; presence of reflux ≥ grade 2	Renal units	80.0	98.9	71.2	0.20
Berrocal 2001	Cystosonography (SH U 508A)	Presence of reflux (micro-bubbles)	MCUG (Plenigraf); presence of reflux	Renal units	90.4	91.4	10.5	0.11
				Patients	88.2	88.6	7.5	0.14
Frutos 2000	Cystosonography (Levograf)	Presence of reflux (micro-bubbles)	MCUG; presence of reflux	Renal units	90.0	91.5	10.6	0.11
Haberlick 1997	Colour doppler cystosonography	Presence of reflux (blue-coloured jet)	MCUG; presence of reflux	Renal units	70.0	91.9	8.7	0.33
Kessler 1982	Cystosonography (Cysto-Conray)	Presence of reflux (micro-bubbles and/or dilation)	MCUG; presence of reflux ≥ grade 2	Renal units	76.5	100.0	58.5	0.24
Mentzel 2002	Cystosonography (Levovist)	Presence of reflux	MCUG; presence of reflux	Renal units	90.0	94.6	16.6	0.11
Piaggio 2003	Cystosonography (Levovist)	Not stated	MCUG; presence of reflux	Renal units	56.8	84.8	3.8	0.51
Radmayr 2002	Doppler Cystosonography (galactose based contrast agent)	Presence of reflux (micro-bubbles)	MCUG; presence of reflux	Renal units	95.9	96.3	25.7	0.04
Rohden 1995	Cystosonography (Echovist)	Not stated	MCUG; presence of reflux	Patients	85.7	100.0	32.5	0.14
Schneider 1984	Cystosonography (Conray FL/air)	Presence of reflux (increased separation in the central renal echo complex)	MCUG; presence of reflux ≥ grade 2	Renal units	87.2	90.0	8.4	0.15
		Presence of reflux	MCUG; presence of reflux	Renal units	73.0	90.4	7.6	0.30

[2] Taken from the Health Technology Assessment 'Clinical and Cost Effectiveness of tests for the diagnosis of urinary tract infection in children: a systematic review and economic model

Siamplis 1996	Cystosonography (air)	Not stated	MCUG; presenc[3]e of reflux	Renal units	83.3	97.5	32.9	0.17
	Cystosonography (fluid)			Renal units	94.4	94.9	17.2	0.08
Valentini 2001	Grey scale Cystosonography (Levovist)	Presence of reflux (micro-bubbles)	MCUG; presence of reflux	Renal units	81.0	94.7	15.4	0.20
	Colour Doppler Cystosonography (Levovist)	Presence of reflux (colour signals)		Renal units	100.0	93.4	13.8	0.01

1

2

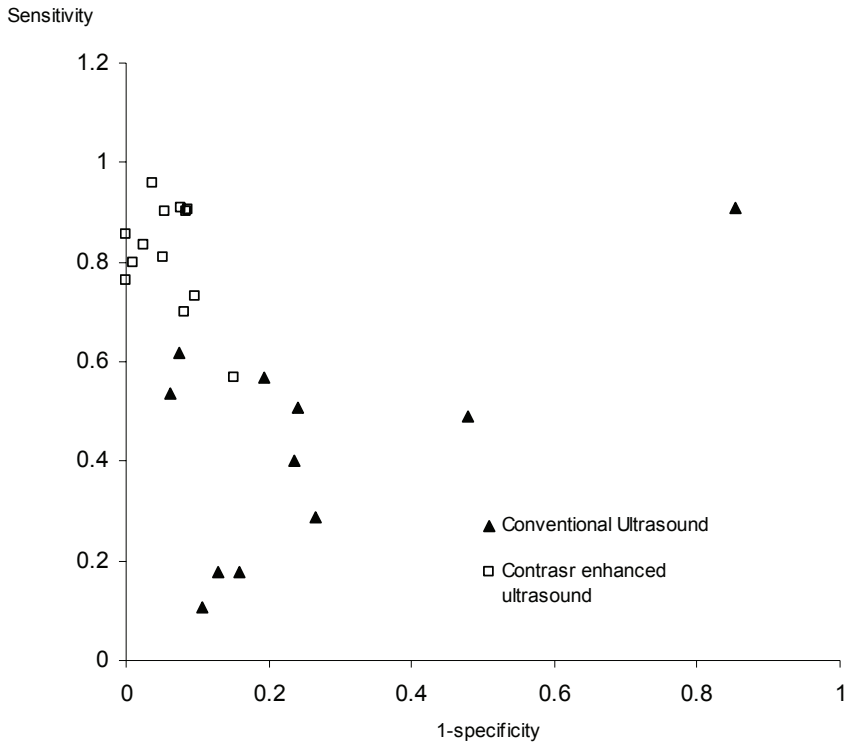
Taken from the Health Technology Assessment 'Clinical and Cost Effectiveness of tests for the diagnosis of urinary tract infection in children: a systematic review and economic model

One study from Japan evaluated the diagnostic potential of voiding urosonography (VUS) (cystosonography) compared with MCUG conducted simultaneously.[219]

Boys and girls 1 month to 14 years (mean age 2.3 years) with confirmed UTI and follow-up of previously detected VUR underwent simultaneous VUS and MCUG. The sensitivity was 86%, specificity 95%, PPV 86% and NPV 95%. When a subgroup of children under 24 months of age were analysed the sensitivity decreased to 73% and specificity increased to 98%. PPV increased to 92% and NPV decreased to 93%. (n=56 or 111 ureterorenal units (one patient with a single kidney was included).

A study in Albania evaluated the diagnostic efficacy of voiding cystourethrosonography (CUS) (cystosonography) compared to MCUG. 22 children aged 2 months to 14 years (mean age 3.9 years) were referred to hospital for investigation of VUR because of documented acute pyelonephritis. Sensitivity of CUS for detecting VUR was 93%, specificity 44%, PPV 75% and NPV 78%.[220][EL II]

Figure 6.3.1.1 1 Conventional ultrasound vs. contrast enhanced ultrasound plotted in ROC space[4]



6.3.2 DMSA

A systematic review identified two studies evaluating the diagnostic accuracy of DMSA to investigate the likelihood of reflux[132] Both studies were of poor quality; only one reported sufficient information about the index and reference tests and neither reported patient selection criteria. The studies reported sensitivities of 67% and 77% and specificities of 63% and 74%.

[4] Adapted from the Health Technology Assessment 'Clinical and Cost Effectiveness of tests for the diagnosis of urinary tract infection in children: a systematic review and economic model

1 **Table 6.3.2.1 DMSA vs. MCUG[5]**

2

Study details	Test details; time	Definition of positive result	Reference standard; definition of positive result	Unit of analysis	Sens	Spec	LR+	LR-
Oostenbrink 2000	Combined risk score: gender, family history, age, CRP and ultrasound.	≥1	MCUG; presence of reflux	Patients	100.0	15.0	1.2	0.09
		≥6			91.9	37.9	1.5	0.24
		≥11			81.1	52.4	1.7	0.38
		≥16			64.9	71.8	2.3	0.50
		>25			51.4	92.2	6.3	0.53
		≥11	MCUG; presence of reflux > grade 3		89.3	51.8	1.8	0.23
		≥16			71.4	70.5	2.4	0.42
		>25			57.1	90.2	5.6	0.48
Trave 1997	Scintigraphy (Tc-99m-DMSA)	Renal changes indicative of APN	MCUG; presence of reflux	Renal units	76.5	74.2	2.8	0.34
Verber 1988	Scintigraphy (Tc-99m-DMSA)	Presence of renal scarring	MCUG; presence of reflux	Renal units	66.7	62.9	1.8	0.54

3

4

[5] Taken from the Health Technology Assessment 'Clinical and Cost Effectiveness of tests for the diagnosis of urinary tract infection in children: a systematic review and economic model

A Swedish study detecting VUR in 303 infants (163 boys, 140 girls) younger than 2 years with initial UTI investigated with DMSA scintigraphy and voiding cystourethrography (VCU) within 3 months following UTI.[221] VUR was present in 36/163 (22%) of boys and 44/140 (31%) of girls. Sensitivity of DMSA in investigating the likelihood of reflux was 66%, specificity 54%, PPV 40% and NPV 82% [EL Ib]

A study conducted in Italy compared both renal ultrasound and DMSA with MCUG for investigating the likelihood of VUR in children who had a negative prenatal ultrasound, and presented with UTI in the first 2 years of life.[223]
Sensitivity of renal ultrasound to detect VUR was 45%, specificity 30%, positive predictive value was 21% and negative predictive value was 54%. The positive likelihood ratio was 0.6. Sensitivity of DMSA to detect VUR was 63%, specificity 11%, positive predictive value was 60% and negative predictive value was 12%. The positive likelihood ratio was 0.71.[EL III]

6.3.3 IVU

A systematic review identified four studies assessing the accuracy of IVU for investigating the likelihood of reflux using MCUG as the reference standard.[132] Studies were poorly reported; only one provided sufficient detail of the index test or reference standard, 2 did not report patient selection criteria, three did not report enough information to assess review bias. Sensitivity ranged from 28% to 48% and specificity ranged from 73% to 100%.

Table 6.3.3.1 IVU vs. MCUG[6]

Study details	Test details; time	Definition of positive result	Reference standard; definition of positive result	Unit of analysis	Sens	Spec	LR+	LR-
Cavanagh 1983	IVU (Sodium meglumine diatrizoate)	Presence of renal scarring or anatomical abnormality	MCUG; presence of reflux ≥ grade 3	Patients Patients	100.0 44.8	94.1 97.0	14.2 10.2	0.04 0.58
Drachman 1984	IVU	Not stated	MCUG; presence of reflux	Patients	27.8	100.0	53.3	0.72
Redman 1984	IVU (Diatrizoate)	Not stated	MCUG; presence of reflux	Patients	20.5	100.0	68.9	0.79
Verber 1988	IVU (Hypaque or Niopam)	Presence of renal scarring	MCUG; presence of reflux	Renal units	47.9	73.3	1.8	0.71

[6] Taken from the Health Technology Assessment 'Clinical and Cost Effectiveness of tests for the diagnosis of urinary tract infection in children: a systematic review and economic model

6.3.4 Other tests and combinations of tests

A systematic review identified 7 studies investigating a variety of imaging techniques for investigating the likelihood of reflux including indirect voiding radionuclide cystography, and scintigraphy.[132]

Three studies were identified evaluating indirect radionuclide voiding cystography, however they did not provide sufficient information to assess quality. One study evaluating dynamic micturating scintigraphy (tc-99m-DTPA) did not use MCUG as a reference standard. Two studies, one evaluating indirect radionuclide voiding cystography (Tc-99m-MAG3) and one evaluating dynamic micturating scintigraphy (tc-99m-DTPA) used MCUG as the reference standard.

1 **Table 6.3.4.1 Other investigations for VUR**[7]

2

Study details	Test details; time	Definition of positive result	Reference standard; definition of positive result	Unit of analysis	Sens	Spec	LR+	LR-
Bower 1985	Indirect radionuclide voiding cystography (Tc-99m-DMSA)	Presence of reflux	Direct radionuclide voiding cystography (Tc-99m-DTPA renal scan and a delayed voiding cystogram); presence of reflux	Renal units	68.4	97.1	16.2	0.34
De Sadeleer 1994	Indirect radionuclide voiding cystography (Tc-99m-MAG3)	Presence of reflux	MCUG; presence of reflux	Renal units	32.6	100.0	25.0	0.68
Hedman 1978	Dynamic micturating scintigraphy (Tc-99m-DTPA)3.9	Not stated	MCUG; presence of reflux	Renal units	61.9	95.1	11.2	0.41
Misselwitz 1971	Scintigraphy (I-131-o-Hippurat)	Positive for reflux. Semi-quantitative assessment	IVU; presence of reflux	Renal units	97.4	77.0	4.2	0.04
		Positive for reflux. Qualitative assessment		Renal units	89.6	86.6	6.6	0.13
Oostenbrink 2000	Combined risk score: gender, family history, age, CRP and US	≥1	MCUG; presence of reflux	Patients	100.0	15.0	1.2	0.09
		≥6			91.9	37.9	1.5	0.24
		≥11			81.1	52.4	1.7	0.38
		≥16			64.9	71.8	2.3	0.50
		>25			51.4	92.2	6.3	0.53
		≥11	MCUG; presence of reflux > grade 3		89.3	51.8	1.8	0.23
		≥16			71.4	70.5	2.4	0.42
		>25			57.1	90.2	5.6	0.48

3

[7] Taken from the Health Technology Assessment 'Clinical and Cost Effectiveness of tests for the diagnosis of urinary tract infection in children: a systematic review and economic model

A study conducted in Turkey compared MCUG with direct radionuclide cystography in 25 children with recurrent UTI (13 female, 12 male) aged 1.5 months to 15 years.[222] The sensitivity and specificity were 20% and 74%, respectively.[ELIII]

Evidence summary

The likelihood ratios for conventional ultrasound for detecting reflux were significantly heterogeneous, and suggest that ultrasound is a poor test for both confirming or excluding VUR

Contrast enhanced ultrasound showed good diagnostic performance. The likelihood ratios were significantly heterogeneous but they suggest contrast enhanced ultrasound is a good test for both confirming or excluding VUR

There is little evidence about the accuracy of direct radionuclide cystography for the assessment of VUR. However it is very rarely used in the UK. Indirect radionuclide cystography is used frequently to assess reflux in toiled trained children as it avoids the need for bladder catheterisation.

Clinical evidence showed that cystosonography and MCUG were both capable of detecting reflux. One study found that the cost of each test is similar. In the

absence of evidence of long-term treatment outcomes following the use of each test the relative cost-effectiveness of these tests has not been assessed.

Translation

Imaging tests that are able to detect reflux include MCUG, direct and indirect cystography and cystosonography.

If imaging is required to demonstrate the presence of absence of VUR in a child who has had a UTI, then either micturating cystourethrography (MCUG) or contrast enhanced ultrasonography can be used. In toilet trained children indirect radionuclide cystography avoids bladder catheterisation and may be preferable. The choice of test will depend on local expertise and availability and whether or not anatomic information of the bladder outflow tract and urethra is required. In this latter situation MCUG should be done.

Recommendations

Routine imaging to identify vesicoureteric reflux is not recommended in children who have had a urinary tract infection, except in specific circumstances outlined in the tables. (Table 6.7.1 – 6.7.3)

When imaging is required to detect reflux in pre toilet trained boys, an MCUG is recommended so that the urethra is also imaged. In girls cystosonography is a valid alternative.

6.4 Predicting renal parenchymal defects

Studies investigating different techniques for predicting renal parenchymal defects fall into two categories. Studies in which the index test is carried out close to the time of the UTI and the DMSA (reference standard) is carried out at a later date show how well the index tests predicts renal parenchymal defects in a child with UTI. Those in which the index test and the DMSA are carried out at the same time are showing the accuracy of the test for predicting renal parenchymal defects. The following section is presented in this way.

A systematic review identified four studies reporting 9 data sets for the prediction of renal scarring.[132] All studies used follow-up DMSA as the reference standard, however generally were not of good quality. No study reported sufficient details of the index or reference tests.

In evaluating non-invasive indicators including fever and acute CRP as indicators of renal scarring both temperature ≥38°C and CRP showed the same results for predicting renal scarring where sensitivity was 92%, specificity 20%, PPV 41% and NPV 80%.

Two studies (one using Doppler ultrasound and one using IVU) reported sensitivities of 27% and 12% and specificities of 92% and 99%.

1 Table x. MCUG vs. scintigraphy

Study details	Test details; time	Definition of positive result	Reference standard; definition of positive result; time	Unit of analysis	Sens	Spec	LR+	LR-
Stokland 1998	MCUG; not stated	Presence of reflux	Scintigraphy (Tc-99m-DMSA; presence of renal scaring; follow-up	Renal units	40.0	84.6	2.6	0.71
Stokland 1996	MCUG; acute	Presence of reflux	Scintigraphy (Tc-99m-DMSA; presence of renal scaring; follow-up	Patients	47.5	82.5	2.7	0.64
Ultrasound vs. scintigraphy								
Hitzel 2000	Colour Doppler; not stated	Not stated	Scintigraphy (Tc-99m-DMSAnot stated; follow-up	Renal units	65.2	59.6	1.6	0.60
Jequier 1998	Doppler; acute	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA; presence of renal scarring; follow-up	Patients	26.9	91.9	3.0	0.80
	Standard ultrasound; acute				42.6	66.7	1.3	0.86
Other								
Stokland 1996	Temperature; acute	≥38.5°C	Scintigraphy (Tc-99m-DMSA); presence of renal scarring; follow up	Patients	91.5	20.4	1.1	0.44
	CRP; acute	>20mg/L			91.5	20.4	1.1	0.44
Stokland 1998	IVP; acute	Presence of renal scarring	Scintigraphy (Tc-99m-DMSA); presence of renal scarring; follow up	Renal units	12.3	99.2	12.9	0.88
	Scintigraphy (Tc-99m-DMSA); acute				55.4	82.3	3.1	0.54

2

3

One study conducted in Spain compared clinical findings compared to DMSA for distinguishing between UTI with and without renal damage.[224] This study did not report actual numbers for sensitivity, specificity, PPV and NPV and should be interpreted with caution.

Seventy-seven children aged 1 month to 12 years old admitted to a paediatric emergency department with clinical signs (fever and abdominal pain in older children), non-specific signs (irritability or vomiting in younger children) and a positive urine sample were evaluated to assess the value of CRP and procalcitonin in distinguishing between UTI with and without renal damage. Blood was sampled at the time of admission and DMSA was performed 5-6 months later. [EL III]

Table 6.4.1 Summary CRP and procalcitonin[224]

	sensitivity	specificity	PPV	NPV
CRP 20mg/l	92%	34%	23%	95%
Procalcitonin1ng/ml	93%	62%	32%	98%

A study conducted in France compared a semi-quantitative uptake score on acute DMSA (reference standard) with a quantative automatic index to predict renal scarring on follow-up DMSA.[225] Both the intensity and severity and the size and extent of the uptake defect were considered. 43 children (85 kidneys - one child had a single kidney), 3 boys and 40 girls aged 11 months to 15.5 years (mean 5.8 ± 3.6 years) with acute pyelonephritis and who had a DMSA performed at the acute stage were evaluated.

On DMSA one, 59 kidneys were normal and 26 kidneys were abnormal. At the follow up DMSA, the 59 normal kidneys remained normal and of the 26 abnormal kidneys, 14 kidneys had improved and 12 kidneys remained unimproved.

When the intensity and severity threshold of 70% was used, a cut off value of 0.45 was able to predict scarring with a sensitivity of 85%, specificity of 78%, PPV of 85% and NPV of 77%. [EL III]

Evidence summary

There is insufficient information about diagnostic tests for predicting renal parenchymal defects to draw any conclusions about their effectiveness or cost-effectiveness.

6.5 Detecting renal parenchymal defects

6.5.1 IVU

A systematic review identified four studies evaluating the diagnostic accuracy of IVU for detecting renal scarring using a scintigraphic technique as the reference standard.[132] Only one of these studies used and appropriate spectrum of patients and this study reported sensitivity of 22%, specificity of 98%, PPV of 74% and NPV of 83%.

1

2 Table x. IVP vs. scintigraphy

Study details	Test details; time	Definition of positive result	Reference standard; definition of positive result; time	Unit of analysis	Sens	Spec	LR+	LR-
McLorie 1980	IVP (Diatrizoate meglumine and diatrizoate sodium); not stated	Presence of renal scarring	Scintigraphy (Tc-99m-DMSA); presence of renal scarring; not stated	Renal units	82.8	100.0	58.8	0.19
Merrick 1980	IVP; not stated	Not stated	Scintigraphy (Tc-99m-GH or Tc-99m-DMSA); not stated; not stated	Renal units	85.5	100.0	171.3	0.15
Pickworth 1992	IVP; not stated	Not stated	Scintigraphy (dynamic including micturating, Tc-99m-MAG3); presence of renal scarring or reflux; not stated	Patients	59.1	100.0	74.0	0.42
Stokland 1998	IVP follow up	Presence of renal scarring	Scintigraphy (Tc-99m-DMSA); presence of renal scarring; follow up	Renal units	21.5	98.0	10.0	0.80

3

6.5.2 Dynamic renal imaging

A systematic review identified two studies evaluating the diagnostic accuracy of dynamic scintigraphy (MAG3) with DMSA as the reference standard.[132] One study investigated renal units where sensitivity of MAG3 was 88%, specificity 88%, PPV 86% and NPV 90%. The second study investigated MAG3 by patient and found a sensitivity of 82%, specificity 95%, PPV 88% and NPV 92%.

1 Table x. Dynamic vs. standard scintigraphy

Study details	Test details; time	Definition of positive result	Reference standard; definition of positive result; time	Unit of analysis	Sens	Spec	LR+	LR-
Gordon 1992	Dynamic including micturating (Tc-99m-MAG3); follow up	Not stated	Tc-99m-DMSA on follow up; presence of renal scarrin; follow-up	Renal units	88.0	88.3	7.1	0.15
Pickworth 1992	Dynamic including micturating (Tc-99m-MAG3); not stated	Presence of renal scarring or reflux	Tc-99m-DMSA; not stated; not stated	Patients	82.4	94.7	12.6	0.21

6.5.3 MCUG

A systematic review evaluated the presence of reflux (on MCUG) as an indicator of scarring.[132] Three data sets were identified in two studies where DMSA was used as the reference standard. In two data sets evaluating renal units one study investigating follow up MCUG showed a sensitivity of 73%, specificity of 37%, PPV of 44% and NPV of 67% and the second study using acute MCUG showed a sensitivity of 39%, specificity of 82%, PPV of 47% and NPV of 76%. The third data set evaluated patients undergoing acute MCUG and showed a sensitivity of 48%, specificity of 78%, PPV of 64% and NPV of 65%.

1 Table x. MCUG vs. scintigraphy

Study details	Test details; time	Definition of positive result	Reference standard; definition of positive result; time	Unit of analysis	Sens	Spec	LR+	LR-
De Sadeleer 1994	MCUG (iodinated contrast material); follow up	Presence of reflux	Tc-99m-DMSA; presence of scarring; not stated	Renal units	73.1	36.8	1.1	0.75
Ditchfield 1994	MCUG; acute	Presence of reflux ≥ grade 2	Tc-99m-DMSA; renal changes indicative of APN; acute	Patients	47.8	78.3	2.2	0.67

2

6.5.4 Ultrasound

A systematic review identified six studies reporting 8 data sets for detecting renal scarring.[132]

Three studies reported renal scarring results by renal units. Two studies reported sensitivities of 86% and 81%, specificities of 98% and 87%, PPVs of 93% and 81% and NPVs of 95% and 87%. The third study showed much poorer results for the performance of ultrasound in detecting scarring and showed sensitivity of 3%, specificity 97%, PPV 50% and NPV 56%. The reasons for the discrepancies in results are unclear.

A further three studies reported renal scarring results by patient. Sensitivity ranged from 23% to 67%, specificity from 80% to 99%, PPV from 55% to 83% and NPV from 59% to 91%.

1 Table x. Ultrasound vs. scintigraphy

Study details	Test details; time	Definition of positive result	Reference standard; definition of positive result; time	Unit of analysis	Sens	Spec	LR+	LR-
Barry 1998	Ultrasound; 1-3 months	Presence of renal scarring	Tc-99m-DMSA; not stated; follow up	Renal units	86.5	97.7	35.9	0.14
LeQuesne 1986	Ultrasound; not stated	Presence of renal scarring or signs of reflux	Tc-99mj-DMSA; not stated; not stated	Renal units	81.5	87.2	5.8	0.23
MacKenzie 1994	Ultrasound; acute	Any abnormality	Tc-99m-DMSA; renal changes indicative of APN; acute	Patients	52.5	80.4	2.6	0.60
Mucci 1994	Ultrasound; not stated	Not stated	Tc-99m-DMSA; not stated; not stated	Patients	22.7	99.4	27.4	0.77
Scherz 1994	Ultrasound; not stated	Presence of renal scarring	Tc-99m-DMSA; presence of renal scarring; follow up	Patients (asymptomatic)	100.0	95.7	14.0	0.13
				Patients (symptomatic)	60.0	78.6	2.7	0.52
				Patients (all)	66.7	84.6	4.1	0.41
Trave 1997	Ultrasound; acute	Not stated	Tc-99m-DMSA; renal changes indicative of APN; acute	Renal units	3.4	97.3	1.3	0.99

2

A study conducted in the UK investigated the use of ultrasonography in the evaluation of renal scarring.[226] 465 children (930 kidneys) aged 3 months to 16 years with proven UTI who presented to a radiology department and who underwent ultrasound and DMSA on the same day at least 3 months after UTI were included.

The sensitivity of ultrasound to detect focal scarring in kidneys was 5.2%, specificity 98.3%, PPV 50% and NPV 75.8%. The sensitivity of ultrasound to detect diffuse scarring in kidneys was 47.2%, specificity 91.8%, PPV 60.8% and NPV 86.6%.[EL II]

A study conducted in Taiwan evaluated the use of ultrasonography and CRP level in 45 children (31 boys and 14 girls) aged 9 days to 10 years old (mean 1.5 ± 0.2 years, median 0.3 years) with febrile UTI who fulfilled criteria for acute pyelonephritis.[227] The sensitivity of ultrasound to detect renal scarring was 59%, specificity 61%, PPV 59% and NPV 61%. (p=0.11, OR 2.3, 95% CI 0.82 to 7.65). The sensitivity of CRP >70mg/L to predict renal scarring was 81%, specificity 74%, PPV 78% and NPV 77%, (p<0.0001, OR 11.9, 95%CI 3.72 to 38.11). The sensitivity of ultrasound and CRP >70mg/L combined to detect/predict renal scarring was 52%, specificity 81%, PPV 76% and NPV 59%, (p<0.01, OR 4.7, 95%CI 1.47 to 14.95).

A study conducted in Turkey compared the efficacy of DMSA and renal ultrasonography in detecting renal scars in 62 children (18 boys, 44 girls) aged 6 months to 15 years (mean age 5 years) diagnosed with primary VUR between 1997 and 2003 following a documented UTI.[228] Of 90 refluxing units, 33% had grades I to II VUR, 41% had grade III and 26% had grades IV to V. DMSA detected renal scars in 32/58 units with bilateral VUR and in 20/33 units with unilateral VUR. Ultrasonography detected scars in 22/58 units with bilateral VUR (sensitivity 69%, specificity 100%) and in 9/33 with unilateral VUR (sensitivity 45%, specificity 100%). Ultrasound did not detect any defects when DMSA was normal.[EL III]

6.5.5 Other imaging techniques

A systematic review identified two studies, one evaluating the use of magnetic resonance imaging (MRI) techniques and one evaluating MAG3 scintigraphy. Both using DMSA as the reference standard and both reported results by renal units.[132]

The first study evaluated three MRI sequences. Sensitivity ranged from 81% to 100%, specificity from 78% to 91%, PPV from 70% to 81% and NPV from 91% to 100%. The second study evaluated the presence of defects on MAG3. Sensitivity was 46%, specificity 87%, PPV 71% and NPV 70%.

A study conducted in Ireland compared DMSA with MRI for detecting renal parenchymal defects in 37 children (19 boys and 18 girls) aged 4 months to 13 years (mean 4.5 years) presenting for radiological investigation after a first UTI.[229]

The sensitivity of MRI in detecting renal parenchymal defects on a kidney-by-kidney basis where each kidney was graded as normal or abnormal for renal scarring was 77%, specificity 87%, PPV 77% and NPV 87%. The sensitivity of MRI in detecting renal parenchymal defects on a zonal basis where each kidney was divided into 6 zones and each zone was assessed for the presence or absence of renal scarring was 75%, specificity 98%, PPV 83% and NPV 97%.[EL Ib]

A study conducted in Turkey compared MRI with DMSA for localising UTI and detecting scarring in 20 children (15 females, 5 males).[230] Children were aged 2 to 14 years (mean age 7.3 ± 3.4 years) and symptomatic UTI (including dysuria, enuresis, costovertebral pain, fever of <37.5C and/or a positive urine culture). The sensitivity of MRI to demonstrate renal lesions was 91%, specificity 89%, PPV 91% and NPV 89%.

Evidence summary

DMSA is the most accurate method for detecting renal parenchymal defects in children in who have had a UTI.

Translation

From a clinical perspective tests that are able to detect renal parenchymal defects include DMSA, ultrasound, MAG 3 and contrast enhanced MRI.

When a diagnostic test is required for the detection of renal parenchymal defects, ultrasound is less accurate than DMSA. If defects on ultrasound are identified, they appear relatively specific and in the clinical context of a child who has had a urinary tract infection could obviate the need for a DMSA scan. This would be important when considering the burden of ionising radiation involved in imaging following urinary tract infection.

Recommendations

A DMSA scan 6 months following the acute infection should be used to detect renal parenchymal defects as recommended. (Table 6.7.1 – 6.7.3)

If the child has a subsequent UTI while awaiting DMSA the timing of the DMSA should be reviewed.

IVU should not be used routinely to detect renal parenchymal defects in children who have had a UTI.

Research recommendations

MRI appears to be an accurate method of detecting renal parenchymal defects however evidence is limited. Further studies investigating its diagnostic accuracy and cost-effectiveness are required.

6.6 Localisation of infection

6.6.1 Ultrasound

Conventional ultrasound

A systematic review assessed the diagnostic accuracy of ultrasound in 18 studies where renal scintigraphy was the reference standard.[132] In 14 of the 18 studies the scintigraphic standard was DMSA. Of the 18 studies, ten did not use an appropriate spectrum of patients and 4 did not describe criteria used to select patients. 6/18 studies provided an adequate description of both the index test and the reference standard.

Of the 18 studies, sensitivity ranged from 9.2 (specificity 100%) to 93.6% (specificity 50%). However, all but three studies reported sensitivities of below 60%. Specificity ranged from 50% (sensitivity 93.6%) to 100% (sensitivity 9.2% to 50%); all but four studies were above 80%.

Likelihood ratios showed considerable heterogeneity ($p<0.0001$) with positive likelihood ratios ranging from 1.6 (LR- 0.68) to 55.0 (LR+ 12.7) and negative likelihood ratios ranging from 0.10 (LR+ 2.5) to 0.91 (LR+ 12.7). The pooled positive likelihood ratio was 3.1 (95% CI 2.3, 4.3) and the pooled negative likelihood ratio was 0.62 (95% CI 0.53, 0.73).

Calculated predictive values of conventional ultrasound for localising UTI for PPV ranged from 32% to 100% for PPV and ranged from 33% to 86% for NPV.

ROC plots show considerable heterogeneity between studies suggesting that conventional ultrasound is a poor test for the localisation of UTI.

1 Table x. Ultrasound vs. scintigraphy

Study details	Test details; time	Definition of positive result	Reference standard; definition of positive result	Unit of analysis	Sens	Spec	LR+	LR-
Andrich 1992	Standard; not stated	Not stated	Scintigraphy (Tc-99m-DMSA); not stated; not stated	Patients	11.5	100.0	6.5	0.88
Benador 1994 ≥1 yr, any UTI	Standard; acute	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Patients	38.7	66.7	1.1	0.94
≥1 yr, 1st UTI					27.8	33.3	0.5	1.89
≥1 yr, multiple UTI					53.8	83.3	2.5	0.59
<1 yr, any UTI					46.5	85.7	3.0	0.63
<1 yr, 1st UTI					45.0	84.6	2.7	0.66
<1 yr multiple UTI					66.7	100.0	3.8	0.45
All ages, any UTI					43.2	81.1	2.3	0.70
All ages, 1st UTI					39.7	79.3	1.8	0.77
All ages, multiple UTI					56.3	87.5	3.4	0.53
Biggi 2001	Standard; not stated	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Renal units	27.1	88.9	2.4	0.82
Bircan 1995	Standard; acute	Renal changes indicative of APN and presence of congenital abnormalities	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Patients	24.4	100.0	9.5	0.76
Boudailliez 1998	Doppler; not stated	Not stated	Scintigraphy (Tc-99m-DMSA); not stated; acute	Renal units	33.3	88.2	2.8	0.76
Girona 1995	Standard; not stated	Abnormal kidney size	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; not stated	Renal units	45.9	72.9	1.7	0.74
Guermazi 1993	Standard; not stated	Renal changes indicative of APN or scarring	Scintigraphy (Tc-99m-DMSA); presence of acute or chronic lesions; not stated	Patients	42.4	92.8	5.9	0.62
Hajjar 2002	Doppler; acute	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Patients	53.6	95.2	11.3	0.49
Hitzel 2002	Doppler; acute	Renal changes	Scintigraphy (Tc-99m-DMSA); renal	Patients	93.6	50.0	1.9	0.13

		indicative of APN	changes indicative of APN; acute	Renal units	79.6	81.4	4.1	0.26
Hitzel 2000	Colour Doppler; not stated	Not stated	Scintigraphy (Tc-99m-DMSA); not stated; acute	Renal units	84.3	81.7	4.6	0.19
Ilyas 2002	Standard; acute	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Patients	9.2	100.0	12.7	0.91
Jakobsson 1992	Standard; acute	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Renal units	56.5	63.9	1.6	0.69
Jequier 1998	Standard; acute	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Patients	40.6	84.3	2.6	0.70
	Doppler; acute			Patients	19.8	98.4	8.4	0.82
Krzemien 2002	Doppler; acute	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Renal units	46.9	92.3	6.1	0.58
Lavocat 1997	Standard; acute	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Renal units	50.0	100.0	55.0	0.50
Morin 1999	Standard; acute	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Patients	93.5	62.5	2.5	0.10
Sfakianakis 1989	Standard; not stated	Not stated	Scintigraphy (Tc-99m-glugoheptonate); not stated; not stated	Patients	48.0	100.0	23.1	0.52
Sreenarasimhalah 1995	Standard; acute	Not stated	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Renal units	39.6	95.3	8.5	0.63

A study conducted in Taiwan evaluated the use of ultrasonography and CRP level in 45 children (31 boys and 14 girls) aged 9 days to 10 years old (mean 1.5 ± 0.2 years, median 0.3 years) with febrile UTI who fulfilled criteria for acute pyelonephritis.[227]

Table 6.6.1.1 Ultrasound and CRP measures[227]

	sensitivity	specificity	PPV	NPV
ultrasound	49%	88%	91%	40%
CRP >70mg/L	59%	61%	59%	61%
Combined	36%	95%	95%	36%

A study conducted in the USA had two aims; first, to correlate the clinical and laboratory manifestations of acute pyelonephritis with the results of DMSA in different age groups and second to compare DMSA renal ultrasonography and VCUG, using DMSA as the gold standard.[231] 222 children (47 boys, 175 girls) aged 2 to 228 months (median age 55 months). Children were divided into three groups; Group I – 85 children under 2 years old; Group II – 91 children 2 to 8 years old; Group III – 46 children over 8 years old.

Of the children in group I, 41/85 (48%) had an abnormal DMSA, while 44/85 (44%) had a normal DMSA. In group II, 63/91 (69%) children had a abnormal DMSA, while 28/91 (31%) had a normal DMSA; and in group III, 39/46 (85%) children had an abnormal DMSA and 7/46 (15%) normal DMSA. The sensitivity of renal ultrasound to detect renal involvement was 9%, specificity was 100%, PPV was 100% and NPV was 39%.[EL III]

Power Doppler Ultrasonography

A study conducted in Israel investigated Power Doppler ultrasonography (PDU) in children with UTI. Baseline characteristics showed that the mean CRP level was significantly higher in children with acute pyelonephritis than in children with lower tract infection (48.1 ± 39 2mg/L vs 114.9 ± 48.1mg/L, p<0.001). There were no differences in age (p=0.66), gender (p=0.47), white blood cell count (p=0.06) or ESR (p=0.46). For detecting acute pyelonephritis the PDU showed a sensitivity of 87%, specificity of 92%, PPV of 93% and NPV of 86%.(n=57 children with a mean age of 22 months)[232]

An second Israeli study of 40 infants (78 kidneys evaluated) assessed the role of renal power doppler ultrasonography (PDU) to identify acute pyelonephritis.[233] The PDU showed a sensitivity of 74%, specificity of 94%, PPV of 87% NPV 87%. The study went on to compare PDU with DMSA for identifying renal lesions in children who showed acute pyelonephritis on DMSA. The sensitivity of the PDU decreased to 58%.[EL Ib]

6.6.2 MCUG

A systematic review identified 7 studies evaluating the diagnostic accuracy of MCUG to predict the localisation of the infection where DMSA was the reference standard. [132]

Six studies used acute DMSA and one study used follow-up DMSA. Two studies reported sufficient detail of the index test to be replicated, although in general the studies were poorly reported. Three studies did not include an appropriate spectrum of patients and four did not report enough information to assess test review bias.

Sensitivity ranged from 21.6% (specificity 96.2%) to 47.1% (specificity 60%). Specificity ranged from 50% (sensitivity 29%) to 96.2% (sensitivity 21.6%). Five of the seven studies reported estimates of specificity above 80%.

Positive likelihood ratios showed significant heterogeneity ($p<0.001$), however negative likelihood ratios were statistically homogeneous ($p=0.575$). Positive likelihood ratios ranged from 0.6 (LR- = 1.42) to 5.8 (LR- = 0.81). Negative likelihood ratios ranged from 0.72 (LR+ = 2.8) to 1.42 (LR+ 0.6). The pooled positive likelihood ratio was 1.9 (95%CI 1.2, 3.1) and the pooled negative likelihood ratio was 0.8 (95%CI 0.74, 0.87).

ROC curves showed that all studies included indicate that MCUG is a poor test for localising UTI.

Calculated predictive values of MCUG for localising UTI for PPV ranged from 47% to 82% and for NPV ranged from 8% to 82%.

1 Table x. MCUG vs. scintigraphy

2

Study details	Test details; time	Definition of positive result	Reference standard; definition of positive result	Unit of analysis	Sens	Spec	LR+	LR-
Fretzayas 2000	MCUG; acute	Presence of reflux	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Patients	30.0	86.8	2.3	0.81
Girona 1995	MCUG; not stated	Presence of reflux ≥ grade 2	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Renal units	21.6	96.2	5.8	0.81
Ilyas 2002	MCUG; acute	Presence of reflux	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Patients	47.1	60.0	1.2	0.88
Jakobsson 1992	MCUG; follow up	Presence of reflux	Scintigraphy (Tc-99m-DMSA); presence of renal scarring; follow up	Renal units	31.6	83.6	1.9	0.82
Lavocat 1997	MCUG; not stated	Presence of reflux	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Renal units	30.4	88.9	2.7	0.78
Morin 1999	MCUG; acute	Presence of reflux	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Patients	29.0	50.0	0.58	1.42
Stokland 1996	MCUG; not stated	Presence of reflux	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Renal units	38.1	86.4	2.8	0.72

Other imaging studies

A systematic review identified six studies reporting various tests for localising UTI, all using DMSA as the reference standard.[132]

One study assessed the accuracy of gadolinium enhanced MRI and found sensitivity to be 92% and specificity 44%. A second study assessed the accuracy of CT for diagnosing acute pyelonephritis and reported a sensitivity of 56% and a specificity of 100%. Both studies used DMSA as the reference standard, although because there was only one of each of these studies, conclusions cannot be drawn about their usefulness in localising UTI.

Three studies evaluated the performance of IVU using DMSA as a reference standard. The details of the index tests were poorly reported and one study did not include an appropriate spectrum of patients. These studies report sensitivities ranging from 75% to 100% and specificities ranging from 9% to 44%. Given the small number of studies, no conclusions can be drawn about the usefulness of IVU in localising UTI.

One study evaluated cystography using DMSA as a reference standard, however gave no further details of the type of cystography. The quality of the study was poor and the study reported sensitivity of 41% and specificity of 68%. This study

did not provide enough information to evaluate the usefulness of cystography in localising UTI.

1 Table x.

Study details	Test details; time	Definition of positive result	Reference standard; definition of positive result	Unit of analysis	Sens	Spec	LR+	LR-
MR/CT vs. scintigraphy								
Lavocat 1997	CT scan (Sodium meglumine ioxitalamate); acute	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Patients	56.0	100.0	13.4	0.46
Lonergan 1998	MRI (Gadolinium enhanced); not stated	Renal changes indicative of APN	Scintigraphy (Tc-99m-DMSA or Tc-99m-glucoheptonate); renal changes indicative of APN; not stated	Patients	92.0	44.4	1.6	0.21
				Renal units	86.7	69.4	2.8	0.21
Cystography for the diagnosis of APN								
Andrich 1992	Cystography; not stated	Not stated	Scintigraphy (Tc-99m-DMSA); not stated; not stated	Patients	40.6	67.5	1.2	0.88
IVP for the diagnosis of APN								
Bircan 1995	IVP (Sodium meglumindiatrizoate); acute	Presence of anatomical pathologies	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Patients	8.9	100.0	3.7	0.93
Jakobsson 1992	IVP; follow up	Presence of renal scarring	Scintigraphy (Tc-99m-DMSA); presence of renal scarring; follow up	Renal units	42.1	74.6	1.6	0.78
Stokland 1996	IVP; not stated	Presence of renal scarring	Scintigraphy (Tc-99m-DMSA); renal changes indicative of APN; acute	Renal units	10.6	98.5	6.5	0.90

2

Evidence summary

Conventional ultrasound appears to be a poor diagnostic test for localising infection. Power doppler ultrasonography increases the predictive value of ultrasound.

Heterogeneous positive likelihood ratios and homogeneous negative likelihood ratios suggest that MCUG is a poor test for the localisation of UTI.

No conclusions can be drawn about the effectiveness or cost effectiveness of MRI, CT or IVU in localising UTI due to a small number of poor quality studies.

Translation

It is the view of the GDG that MCUG is not an appropriate test for localising UTI in children, however it is included in this review because it formed part of the Health Technology Appraisal.[132]

In the majority of children with urinary tract infection who respond promptly to treatment, differentiation of upper from lower tract infection by imaging is unnecessary, invasive, resource intensive and may be harmful in terms of the radiation burden. Some laboratory tests such as CRP and procalcitonin have

been used and while CRP is not an accurate diagnostic test to localise UTI, children with acute pyelonephritis are more likely to have raised CRP and procalcitonin.

For these reasons, the GDG considers that clinical and laboratory features are sufficient in the routine management of children with UTI in differentiating those with upper and lower UTIs.

When acute imaging is performed then, ultrasound, including power doppler evaluation should be used because it is readily available, less invasive and does not involve ionising radiation.

Recommendation

The routine use of imaging in the localisation of a urinary tract infection is not recommended.

In the rare instances where it is clinically important to confirm or exclude upper tract infection a DMSA scan is recommended.

If ultrasound is being performed during the acute infection to identify structural abnormalities the power doppler function should be used as it may provide additional information about renal parenchymal involvement.

Research recommendation

Further research on MRI for localising UTI could be considered.

6.7 Recommendations for routine imaging

The following recommendations are based on a consensus reached by the GDG. This has been based on the evidence that has been provided with regard to the relative performance of the various imaging investigations and the opinion of the GDG in the absence of evidence about their utility and impact.

Recommendations

Children who are systemically well only need ultrasound (within six weeks) if they are younger than six months of age or have had recurrent infection. No other investigations are required for any child who is systemically well unless they have recurrent UTI and abnormality on ultrasound in which case late DMSA should be considered.

Children who are systemically unwell should be imaged according to the following tables.

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Table 6.7.1 Infants aged 0 to 6 months

Test	Responds well to treatment	Severe or atypical UTI	Recurrent UTI
Early Ultrasound	N	Y	Y
Late ultrasound	Y (within 6 weeks)*	N	N
Early DMSA	N	N	N
Late DMSA	N	Y**	Y
MCUG	N	Y***	Y***

*If abnormal consider MCUG

**Late DMSA in children with severe or atypical illness and those who responded poorly to treatment is to assess the level of renal damage.

*** When MCUG is performed, prophylactic antibiotics should be given orally for 3 days with MCUG taking place on the second day

Table 6.7.2 Children 6 months to toilet trained

Test	Responds well to treatment	Severe or atypical UTI	Recurrent UTI
Early Ultrasound	N	Y	N
Late ultrasound	N	N	Y
Early DMSA	N	N	N
Late DMSA	N	Y	Y
MCUG	N	N*	N*

* While MCUG need not be performed routinely it should be considered if the following features are present:

- Poor urine flow
- Family history of VUR.
- Non E.coli infection
- Dilatation on ultrasound

Table 6.7.3 Children toilet trained and older

Test	Responds well to treatment	Severe or atypical UTI	Recurrent UTI
Early Ultrasound	N	Y*	N
Late ultrasound	N	N	Y
Early DMSA	N	N	N
Late DMSA	N	N	Y

MCUG	N	N	N

*Ultrasound in toilet-trained children should be performed with a full bladder with an estimate of bladder volume pre and post micturition.

Definitions

Atypical UTI: Still febrile after 48 hours of appropriate treatment, poor urine flow or non-E.coli

Recurrent UTI: Two or more episodes of UTI with systemic symptoms/signs or three or more episodes of UTI without systemic symptoms/signs.

Early ultrasound: During the acute episode.

Late ultrasound: Within 6 weeks

Early DMSA: During the acute illness

Late DMSA: Six month or more following the acute infection

MCUG: Prophylactic antibiotics should be given for 3 days with MCUG taking place on the second day.

7 Surgical intervention for VUR

Children with vesico-ureteric reflux (VUR) have traditionally been regarded as being more likely to get urinary tract infection, and having an increased risk of developing renal damage. Therefore in every child where it was diagnosed, VUR was corrected with reimplantation surgery. An alternative treatment with antibiotic prophylaxis was then developed with the aim to keep the child free from infections, until the VUR resolved or the risk of renal parenchymal scarring diminished.

The spontaneous resolution of VUR has been clearly described with the large majority of reflux disappearing but sometimes taking 10 years to do so. During the last decade with the advent of prenatal diagnosis of kidney malformations it has become clear that a large proportion of the kidney damage seen in relation to VUR is congenital and part of the same malformation as the reflux.

Diagnosis of VUR is most often by MCUG requiring catheterisation which is unpleasant for children and their parents/carers, carries iatrogenic risks and exposes the child to radiation. The American Academy of Paediatrics Committee[234] recommends an MCUG for all children two months to two years of age after a first time febrile UTI, under the assumption that prophylaxis and/or surgical intervention are beneficial to children who are found to have VUR.

Prophylactic antibiotics have not been shown to reduce the number of recurrent infections and can lead to bacterial resistance. Parents/carers and children can also be non-compliant.

Current indications for surgery in the UK are symptomatic breakthrough UTIs despite medical management and/or increased renal scarring. Surgical interventions incur the risk of anaesthetic and postoperative complications. The open cross trigonal ureteric advancement procedure devised by Cohen remains the favoured operation because of its greater than 95% success rate and low incidence of post-operative ureteric obstruction, but it does require bladder drainage post-operatively.[235] The extra vesical antireflux operation originally described by Lich and Gregoir is another open procedure, unsuited to dilated ureters and as with the Cohen procedure, may require up to a week in hospital.
A recent development is the Submucosal Teflon injection (STING)[236] which is the endoscopic treatment of reflux. This involves an injection of a substance, initially Teflon, and now most often Deflux (polymer of dextran), under the bladder mucosa in the base of the refluxing ureteric orifice. Successful correction of VUR with a single injection is reported as 75%, and can be done as a day case.

The economical and psychological costs of both diagnosing and treating VUR are considerable. The rationale of diagnosing and treating VUR in children with UTI has therefore recently come into question.

A systematic review[215] evaluated the benefits and harms of different treatment options for primary VUR. Seven studies were identified comparing the effectiveness of long-term antibiotic prophylaxis for 1 to 24 months and ureteric re-implantation by surgery.

Antibiotic prophylaxis vs. surgical management, outcome UTI

Seven trials compared prophylaxis with surgical management with the outcomes of UTI. The frequency of recurrent UTI ranged from 0-42% in the antibiotic only group and from 20-22% in the surgical management group.

By two years there was no reduction in the risk of UTI in the surgical management vs. the antibiotic only group (RR1.07, 95%CI 0.55 to 2.09). By five years there were no significant differences in the risk of UTI between the groups (RR 0.99, 95%CI 0.79 to 1.26)

The risk of febrile UTI reported by the European and USA arms of the International Reflux Study was significantly lower in the surgical management group (8-10%) than in the antibiotic only groups (22%) (RR 0.43, 95%CI 0.27 to 0.70). The overall incidence of symptomatic UTI (reported only by the European arm) showed no significant difference between the groups (RR 0.95, 95%CI 0.67 to 1.35)

Antibiotic prophylaxis vs. surgical management, outcome renal parenchymal abnormality

Seven trials compared prophylaxis with surgical management with the outcomes of renal parenchymal abnormality.

Table 7.1 Prophylaxis vs. surgery, outcome renal parenchymal abnormality

	2 years		4-5 years	
	Patients	Individual kidneys	Patients	Individual kidneys
New renal parenchymal abnormality	RR 1.06, (95%CI 0.33 to 3.42)	RR 1.03, (95%CI 0.31 to 3.37)	RR1.09, (95%CI 0.79 to 1.49)	RR 0.85 (95%CI 0.24 to 3.09)
Progressive abnormality	No trials identified	RR 1.56 (95%CI 0.24 to 10.08)	RR 0.99 (95%CI 0.69 to 1.42)	RR 0.84 (95%CI 0.50 to 1.41)
Total new and progressive	No trials identified	1.54 (95%CI 0.24 to 9.95)	RR 1.05 (95%CI 0.85 to 1.29)	RR 0.84 (95%CI 0.53 to 1.34)

The risk of renal parenchymal abnormality at 5 years using DMSA was investigated in the European arm of the International Reflux Study where no differences were found between the antibiotic group and the surgical management group (RR 0.97 95%CI 0.58 to 1.62).

The European and USA arms of the International Reflux Study differentiated between renal scarring and renal parenchymal thinning on IVU. There were no differences at 5 years (RR 1.28 95%CI 0.84 to 1.94) or at 10 years (RR 0.90 95%CI 0.46 to 1.75).

Evidence summary

When compared with prophylaxis primary surgical management of VUR offers no added benefit in prevention of recurrent infections or preventing development of new scars.

Translation

There was one randomised controlled trial comparing endoscopic submucosal ureteric injection (STING) with prophylaxis. Further trials are currently underway comparing the outcomes of the STING in high grade dilating reflux, with prophylaxis and placebo. Studies evaluating the long term benefits of the STING are pending, but in children where surgical treatment of reflux is judged to be necessary, this procedure might be an option.

Recommendations

Surgical management of reflux with or without urinary tract infection is not routinely recommended.

Research Recommendation

Well designed randomised placebo controlled trials are required to determine how effective prophylaxis or various surgical procedures for the management of VUR are in preventing recurrent urinary infection or renal parenchymal defects.

8 Follow up

Historically, follow up has played an important part in our understanding of the natural history and effects of various forms of management of UTI, VUR and renal damage.

The concept of follow up for children with urine infection emerged following the discovery that many children with UTI had recurring infections and underlying renal and urological anomalies. These included characteristic focal pyelonephritic scars or small kidneys seen on IVU and vesicoureteric reflux seen on MCUG. Progression of scarring was observed on serial imaging. Some cases, particularly those with bilateral scarring or small kidneys developed significant hypertension and renal impairment. These conditions had serious implications for morbidity and mortality in later childhood and adult life. Pregnancies complicated by acute pyelonephritis, hypertension, proteinuria and anaemia were also reported.

Follow up appointments were used for a range of strategies including:

- organisation and explanation of imaging tests and conveying the results
- advice on diagnosis and treatment of recurrent UTI
- screening the urine for covert infection
- advice on prevention of recurrence

- management of prophylaxis
- reinforcing advice and preventative strategies
- advice on the risks and consequences of renal scarring
- monitoring the presence of VUR by sequential imaging
- referral for surgery to correct VUR if failed medical management
- advice on familial renal disease including VUR
- blood pressure monitoring for children with renal anomalies
- assessment of renal function and proteinuria as markers of CKD
- a need to understand the natural history of this condition
- a need to understand the effects of various interventions

The exact detail of follow up varied with time, place, access to imaging and individual preference.

Modern healthcare takes a more focussed approach, giving patients and families more information and choice, devolving care locally whenever possible, minimising interventions to those that have been shown to be effective as far as possible and having a more formal and structured approach to research.

However careful the follow up this cannot ensure prompt treatment of recurrent infection as this rarely occurs at the time of a routine clinic appointment. This requires that the patient, primary care system and local hospital are all involved

in the process of recognising the symptoms, establishing the diagnosis and ensuring prompt treatment.

The role of this section is to draw on the evidence of this guideline to consider what follow up is worthwhile and what is no longer appropriate. It is also complementary to the advice of the Renal NSF which recommends that patients with CKD should receive appropriate follow up and assessment. This includes any child with a congenital or acquired renal parenchymal defect. The potential benefits of such follow up need to be set in perspective against other more common, potentially preventable but serious health problems.

Translation

Giving advice and information has been a major part of the follow up process. Now that advice is given earlier and backed up by written information this should not be the sole reason for follow up in most cases.

The use of follow up to order and explain imaging tests and impart the results is largely inappropriate in the light of the reduction of imaging tests proposed. When imaging is indicated, in the majority of cases, this information can be provided both verbally and in writing at the time of diagnosis and treatment of the acute infection. Normal results can be explained by letter.

When an abnormality is detected (or a child has CKD) the child and family will benefit from a discussion with an appropriate paediatric specialist to explain the condition and any associated risks in more detail. Suitable long term arrangements should be made such as monitoring within primary or secondary care.

Children who have frequently recurrent infections will benefit from specialist advice and management to reduce the risk of recurrence. Recurrent attacks of acute pyelonephritis are of particular concern. Some families are particularly anxious because of a family history of VUR or other serious renal problems and need sufficient time combined with accurate information about the condition and its mode of inheritance.

Recommendations

Children who do not undergo imaging investigations should not routinely be followed up.

Parents/carers should be informed of the results of the investigations in writing.

When results are normal, an outpatient appointment is not necessarily required.

Children who have recurrent urinary tract infections or abnormal imaging investigations should be seen by a paediatric specialist. Follow up should include height, weight, blood pressure and routine testing for proteinuria.

Children who have bilateral renal abnormalities, impaired kidney function, raised blood pressure and/or proteinuria should receive monitoring and appropriate management by a specialist to slow the progression of chronic kidney disease.

Children who are asymptomatic following an episode of urinary tract infection should not routinely have their urine re-tested for infection.

Asymptomatic bacteriuria is not an indication for follow up.

9 Advice to children and young people, parents and carers

Urinary Tract Infection is a common bacterial infection which often causes illness in infants and young children. For some young people this may continue into adulthood.

Urinary tract infection is sometimes regarded as unimportant. However a severe infection can make a child extremely unwell and may sometimes have serious consequences and minor infections can be distressing.

Awareness of childhood urinary tract infection in the general population and its signs and symptoms is key to reducing the risk associated with childhood urinary tract infections and it ensures that parents and carers act quickly and appropriately when their child is unwell by seeking help and taking their child to their GP.

One study was identified assessing parental/carer understanding of UTI.[237]

A study conducted in the UK assessed parents/carers understanding of UTI in their child and identify any delay perceived in the diagnosis, along with identifying how helpful parents/carers had found any information they had been given.[237] 52

parents/carers of children aged over two years being investigated in one outpatient department following proven UTI between 1998 and 2000 were evaluated. All children were new referrals and were at their first clinic visit.

87% of parents/carers felt that they had been given an explanation about the need to test for UTI. 52% received a leaflet about childhood UTIs and all parents/carers who received a leaflet found it helpful. 40% of parents/carers felt that clean catch was the easiest method for collecting urine from their child, while 37% used urine collection bags and 23% used urine collection pads.

Content analysis of the qualitative data identified some key themes

Delays in requesting urine samples; Some parents/carers felt there had been a delay between their child becoming unwell and a urine sample being requested.

Difficulties in collection; Mainly around bag collection methods which some parents/carers said produced unnecessary discomfort for their child, while others felt it was difficult to keep the bag in place.

Information; Some parents/carers were happy with the information they received, however the majority requested more information and more detailed advice.

Empowering; Following the initial event, parents/carers in this study seemed to understand more about the diagnosis and felt in a better position to deal with future episodes of UTI in their children. Some parents/carers suggested that their experience taught them what to do in the future.

Organisational problems; A number of parents/carers expressed frustration at organisational aspects in terms of limited GP resources in the weekend, several

hospital appointments for investigations and receiving different information from different health care professionals.[EL 4]

9.2.1 Key Issues

Because urinary tract infection is a common illness for many children advice needs to be given to all parents/carers equally, in much the same way as other advice is given on common childhood illnesses such as measles, chickenpox and meningitis.

The best time to provide advice to parents/carers is whilst their child is still very young and being seen regularly by a midwife, health visitor and or GP. Ensuring that parents/carers are made aware of the signs and symptoms to look for and that they act quickly and appropriately. Professional child carers should also be made aware of the signs and symptoms of childhood urinary tract infections and the need to act promptly and treat quickly.

Children and young people themselves should also be able to access information in a format they can understand.

Information considerations should include:

- Age appropriate format

- In appropriate language (plain English or in an appropriate foreign language)

- Comprehensive advice regarding appropriate treatment choices

- Providing an advice sheet about childhood urinary tract infection in antenatal/post natal information

- Accessible information for all groups of children, young people and parents/carers including accessible information for families with disabilities such as Braille/spoken taped information.

- Where advice can be accessed, hospital/GP surgery/school/youth club/nursery/playgroup etc.

- Clear explanatory diagrams should be included

9.2.2 Advice/Information should be given on:

Symptom recognition and testing

- What the signs/symptoms of urinary tract infection are in the various age groups.

- How to collect urine samples.

- When to seek medical help.

- Types of tests used to establish a urine infection.

Treatment options

Information should be provided which covers treatment in a clear and comprehensible way for all individuals.

Parents/carers and young people should be able to understand the type of treatment necessary, having been partners in the decision making process, and being enabled to make appropriate choices fully aware of all the options.

Prevention

General advice on what a urinary tract infection is, how common it is and 'best practice' for prevention.

Investigations

If any urinary tract investigations are considered, it is necessary to explain to children, young people and parents/carers:

- the reason(s) for investigations
- the details and practical aspects of the investigation(s) proposed
- how the results will be given

Prognosis

Information to children, young people and parents/carers needs to include:

- Risk of recurrent infection
- Risk of renal or urinary tract abnormality
- The implications of any abnormalities found
- The reason for long term follow up if required

Recommendations

Healthcare Professionals should ensure that when a child or young person has been identified as having a possible urinary tract infection they are given appropriate information about the need for treatment, the importance of following any course of treatment through and advice around prevention

Healthcare professionals should ensure that children and young people, parents and carers, are aware of the possibility of a urinary tract infection reoccurring and that they should seek prompt treatment for any suspected re-infection.

Healthcare professional should give advice/information on:

- Prompt recognition of symptoms & urine collection and testing
- Appropriate treatment options
- Prevention
- The nature of and reason for any urinary tract investigation
- Prognosis

Appendix A Estimating risk of end stage renal disease

It has long been assumed that the risk of a first time childhood UTI progressing to long term kidney damage is significant. In investigating the relationship between UTI and long term damage, we are primarily concerned with ESRD, as the relationship between UTI and other potential morbidities is ambiguous and in most cases, not measurable. Whether kidney damage results from VUR alone or in combination with UTI remains uncertain.

Stark[103] has argued that the number of patients who have a single UTI in childhood who then go on to have end-stage renal disease is small, and that the risk of ESRD following a UTI is low. From this position, he argues that the investigations undertaken to diagnose VUR and kidney scarring in children who have experienced a first-time UTI are unwarranted. He estimates that between 10,000 and 15,000 girls would need to be investigated to prevent a single case of ESRD.

Estimating risk

The assumptions used in the model developed by Stark result in a much lower risk that a first-time UTI in childhood will lead to ESRD than was previously assumed. Accepting the risk presented by Stark would lead to a significant change in clinical practice in the NHS and it is important that such a change in

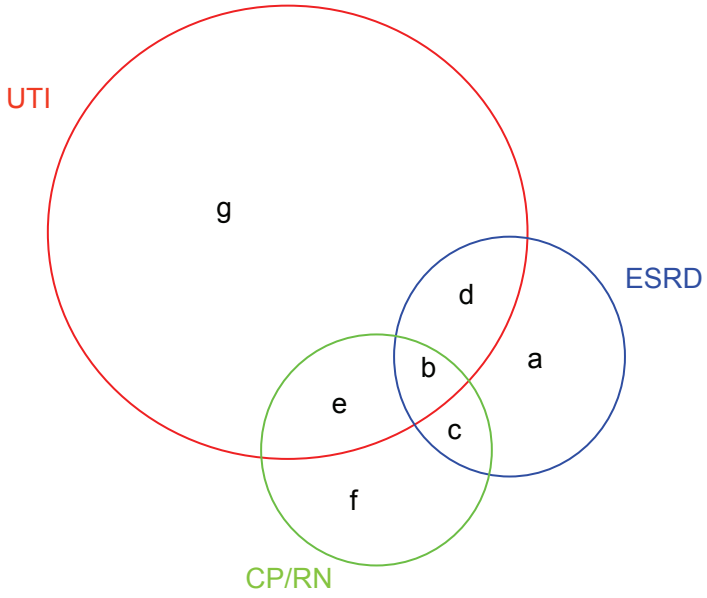
practice be supported by robust evidence. The question that must be addressed is whether we can identify with confidence the true level of risk that a patient with a first-time UTI will develop ESRD as a direct result of that infection.

In order to examine whether this is the case, a model was developed using the assumptions made by Stark to assess the risk of a first UTI in childhood leading to ESRD at any time. The model is represented graphically by the Venn diagram. There is a population of patients with UTI (b+d+e+g), a population of patients with ESRD (a+b+c+d) and a population of patients with CP/RN (b+c+e+f). The proportion of patients in which we are interested is b+d/(b+d+e+g) – that is, the risk of a patient developing ESRD given that they have had a UTI. Using the figures given by Stark the risk is calculated as about 1/10,000, where:

Lifetime risk of UTI (b+d+e+g) = 80,000 per million population (pmp)

Incidence of ESRD (a+b+c+d) = 87pmp

ESRD attributable to CP/RN (b+c) = 9% (0.09)



To calculate the risk, Stark makes two key assumptions. Firstly, that in all cases of ESRD attributable to CP/RN the patient has had a UTI (c=0), and secondly, that CP/RN is the only mechanism by which UTI can lead to ESRD (d=0). The proportion of patients with CP/RN that do not go on to develop

ESRD (f+e) is not of importance. The proportion of ESRD attributable to CP/RN, where c=0, is

(b) * (a+b+c+d) = 0.09 * 87pmp = 8pmp

Therefore the risk of UTI leading to ESRD, where d=0 is:

(b) / (b+e+g) = 8pmp / 0.08 = 100pmp = 1/10,000

During the development of the model, questions were raised about a number of the crucial assumptions made by Stark, primarily the estimate of ESRD incidence and the links between CP/RN and ESRD and between UTI and CP/RN. These assumptions and their implications for the results of the model are examined below.

Estimating the incidence of ESRD

Stark assumes that the statistical risk of a person developing ESRD in their lifetime will be very close to the mean incidence of ESRD during that person's lifetime. Rate of acceptance for Renal Replacement Therapy (RRT) is used as proxy for the rate of ESRD in the absence of accurate data on the number of people that develop ESRD. In the initial analysis undertaken for the guideline, this assumption was not challenged. However, the estimate of 87pmp used by Stark for incidence was an estimate of annual incidence and reflects not the likelihood of an individual developing ESRD during their lifetime but the likelihood of them developing ESRD in a given year. Annual incidence has been used where cumulative incidence was the appropriate measure.

In the absence of a reliable published estimate of the true lifetime risk of developing ESRD, a table was constructed to model a cohort of 1,000,000 patients to determine the number that would develop ESRD in their lifetime. Estimates of risk shown in the table below are reported as annual incidence per million population for females and applied to the proportion of the cohort at risk (those who were alive and who had not already developed ESRD). It is worth noting that males have a greater lifetime risk of ESRD than females. The lifetime risk for males under 60 is nearly 3800pmp compared with about 2500pmp in females. Data for females is used in this analysis to allow comparison with the previous estimate by Stark, but simply substituting the data for males, or for the total population, into the above model will alter the estimate of risk accordingly.

Table 1 shows how the lifetime estimate of developing ESRD was calculated, using data for females from the European Dialysis and Transplant Association (EDTA). The estimated lifetime risk of developing ESRD from this calculation is nearly 6,000 pmp. This represents a much greater risk of developing ESRD than that presented by Stark with significant implications for the model. Substituting the whole life-time estimate based on the data from the EDTA into the formula (a+b+c+d), life-time risk for females developing ESRD as a result of having had a childhood UTI is estimated at about 1/155. The age group of interest is represented by those patients under 60, as it is believed that ESRD that occurs after this age is unlikely to be attributable to a childhood UTI. In this group, the risk of developing ESRD is approximately 2,500 pmp. For that group of patients under 60 where, the risk of UTI leading to ESRD is about 1/355. Estimates of risk

then range from 1/155 to 1/10,000, and the considerable uncertainty in other model parameters must also be explored to illustrate why no reliable estimate of risk can be achieved based on the available data.

Cumulative incidence of ESRD: Females (Source: EDTA)

Age band	Number at start	Mortality rate per million per year	Number at end	Number at risk	Annual incidence of ESRD per million	Number with ESRD (new)	Cumulative ESRD
0 to 1	1000000	4940	995060	997530	8.5	8	8
1 to 4	995051.5	240	994096.3	994573.9	8.5	34	42
5 to 9	994062.5	106	993535.6	993799	8.5	42	85
10 to 14	993493.4	106	992966.8	993230.1	8.5	42	127
15 to 19	992924.6	248	991693.4	992309	8.5	42	169
20 to 24	991651.2	248	990421.6	991036.4	38.2	189	358
25 to 29	990232.3	436	988073.6	989152.9	38.2	189	547
30 to 34	987884.6	436	985731	986807.8	38.2	188	736
35 to 39	985542.6	952	980851.4	983197	38.2	188	923
40 to 44	980663.6	952	975995.6	978329.6	38.2	187	1110
45 to 49	975808.8	2509	963567.3	969688	98.8	479	1589
50 to 54	963088.2	2509	951006.3	957047.3	98.8	473	2062
55 to 59	950533.5	5918	922407.2	936470.4	98.8	463	2525
60 to 64	921944.6	5918	894664.3	908304.4	98.8	449	2973
65 to 69	894215.6	16701	819544.1	856879.8	224.3	961	3934
70 to 74	818583.1	16701	750227.3	784405.2	224.3	880	4814
75 to 79	749347.6	51252	557319.8	653333.7	169.2	553	5367
80 to 84	556767.1	51252	414089.9	485428.5	169.2	411	5777

The causal relationship between UTI and ESRD

Uncertainty in two other key assumptions in the analyses by Stark and the GDG, call into question the strength of the relationship between UTI and ESRD and need to be addressed. These are - the relationship between CP/RN and UTI, and the proportion of ESRD that can be attributed to CP/RN. These are addressed below.

UTI and CP/RN

In all of the analyses presented to date it is assumed, in those cases of ESRD where CP/RN is believed to be the cause, that all patients have also had a UTI. However, no evidence has been presented in support of this assumption. In the analysis by Stark, this assumption is not explicitly stated, although it is evident from the results. In making this assumption, the risk of a UTI leading to ESRD is overestimated – in fact, if the converse is true and no patients with ESRD caused by CP/RN had a UTI in childhood (unlikely though it is), then the risk of UTI leading to ESRD is non-existent. It is not possible, based on current evidence, to estimate the true proportion of patients in whom ESRD is attributed to CP/RN and who have had a UTI in childhood.

In the absence of a reliable estimate of this relationship, it is not possible to make a reliable estimate of overall risk. This can be illustrated using the lifetime risk data in the above table. If the proportion of CP/RN that is associated with UTI is assumed to be 0 the risk of UTI leading to ESRD is equal to 0, though when the proportion of CP/RN that is associated with UTI is assumed to be 1 the risk that

UTI will lead to ESRD in females is 1/155. The range of risk estimates generated is so great, that in the absence of accurate data on the link between CP/RN and UTI, no conclusions can be drawn about the true risk of UTI leading to ESRD.

CP/RN and ESRD

In addition to the uncertainty around the link between UTI and CP/RN, there is also uncertainty over the proportion of ESRD that can be attributed to CP/RN. Stark assumes this rate is nine per cent, using an approximate average of published estimates that are based on data from various renal registers, including European and The United States. In many cases renal registry data is not classified in such a way that a reliable estimate of those cases of ESRD attributable to CP/RN can be made. In contrast to the estimate of nine per cent assumed by Stark, the current proportion of ESRD that is attributed to chronic pyelonephritis/reflux nephritis in the United States Renal Data System 2003 report is 0.46 per cent, or roughly one in every 200 cases of ESRD. The European Dialysis and Transplant Association estimate that eight per cent of all cases of ESRD in England and Wales can be attributed to a more generic classification of pyelonephritis. It is not clear what proportion of this is CP/RN. The wide range of estimates for the likelihood of CP/RN being attributable as the cause of ESRD introduces further uncertainty in the model.

This uncertainty further decreases the reliability of any estimate of the risk of UTI leading to ESRD. Again, using lifetime risk data in the above table, if it is

assumed that eight per cent of ESRD cases are attributable to CR/RN, the risk of UTI leading to ESRD is 1/155. When 0.50 per cent of cases of ESRD are attributed to CP/RN, then the risk is approximately 1/2800. Once again, the range is sufficiently wide to prevent a reliable estimate from being made based solely on the currently available data.

Implications

Given the degree of uncertainty around the key assumptions and data used by Stark, and in turn by the GDG, no reliable estimate of the risk of UTI leading to ESRD can be calculated. It is not clear what the true rate of ESRD caused by CP/RN is, nor is it clear what proportion of these cases have had a UTI in childhood. Without reliable estimates of these figures, as well as of lifetime risk, the level of uncertainty in the model is such that no reliable conclusions can be drawn based on the data alone.

Index

This is normally created by the RCOG Publications Department after guideline sign-off. The NCC-WCH is consulting the Publications Department to establish how the formatting of draft guidelines affects pre-publication editing and typesetting of full guidelines.

1 Evidence tables

2 Predisposing factors

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Ginsburg CM;McCracken GH; 1982 Apr [104]	Study Type: Case-series Evidence Level: 3	To present clinical and laboratory features of UTI	100 infants 62 boys 38 girls	Infants aged 5 days to 8 months (mean 2.1 months) admitted to one of two hospitals with acute UTI from Mar 1976 to Feb 1981	Number with UTI Age at UTI Signs and symptoms at presentation	Male infants accounted for 75% of UTI cases within the first three months of life compared with 11% of boys who were 3 to 8 months of age. Of the 41 infants who were under 30 days old, 33 (81%) were boys. Signs and Symptoms Fever was the most common symptom (in 63%) and symptoms of irritability (55%), had refused feeds (38%), vomiting (36%) and diarrhoea (31%). 67 infants had a fever of ?38?C and 38 infants had fever of ?39?C. Abdominal distention and jaundice were only reported in 8% and 7% of patients respectively.	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Kunin CM;Southall I;Paquin AJ; 1960 [105]	Study Type: x-sectional. Evidence Level: 3	To determine the age, frequency, sex and race distribution of UTI in school aged children Presence of UTI assessed initially by clean catch, confirmed by repeat clean catch and then catheter; UTI defined by 50,000 cfu/ml or more.	n=3057 school children (1647 male, 1410 female)	Participants were from all children enrolled in public, private and parochial schools in a city, 1st through 12th grade (aged approx 6 through 17 yrs), from which 85% 3057/3592) participated in this study One school had black students only (235/260 participated)	No. with ≥100,000 cfu/ml No. with first UTI, by age group No. with UTI for Black females (≥100,000 cfu/ml)	0/1647 boys had >10^5cfu/mL after 2nd clean catch 15/1410 girls continued to have >100,000 cfu/ml after catheterisation 2/15 girls with UTI had had previous UTI (aged 7 and 8) For 6 to 10 age group: 8/772 girls (1.0%); for 11 to 15 age group: 4/495 girls (0.8%); remaining girl was aged between 16-20 yrs. Black females 0.9% (out of 115)	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Biyikli NK;Alpay H;Ozek E;Akman I;Bilgen H; 2004 Feb [106]	Study Type: Case series Evidence Level: 3	To analyse clinical presentation, causative agents, imaging findings and recurrence rates. Clinical presentation only presented in this table (other sections of this paper presented in relevant chapters).	71 neonates with UTI 54/71 (76%) boys and 17/71 (24%) girls	Neonates aged 18.1(±11.2 days) treated for UTI between 1999-2000 at hospital, followed up for at least 6 months, excluded neonates with spina bifida UTI diagnosed as growth of the microorganisms over 10000 cfu/ml in a cateterized urine specimen. Nosocomial UTI defined as a positive urine culture detected 48 hours after admission.	Risk of UTI when pre-term v. not pre-term Assessed by Chi square.	29/71 (41%) were preterm (gestational age 27-37 weeks) 3/71 were small for gestational age Signs and symptoms Signs of sepsis 15/29 (53%) preterm neonates, Hyperbilirubinemia 8/29 (26%) preterm neonate Asymptomatic 6/29 (21%) Hyperbilirubinemia 24/42 (57%) term neonates Signs of sepsis 15/42 (36%) term neonates Asymptomatic in 3/42 (7.1%) The signs of sepsis were: irritability 11/71 (15%) fever or hypothermia 6/71 (8%) respiratory distress 6/71 (8%) feeding problems 4/71 (5%) vomiting 3/71 (4%) abnormal crying 3/71 (4%) poor weight gain 2/71 (2%) rash 1/71 (1%) Asymptomatic 9/71 (13%)	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Jodal U; 1987 Dec [37]	Study Type: Case-series Evidence Level: 3	Study 1 Aims unclear	1177 children with first time symptomatic UTI (952 girls and 225 boys)	Children aged under ten years with first time symptomatic UTI. Bacteriuria definition: At least 10^5 bacteria per ml together with leukocyturia in a midstream sample or bag sample. Any growth on SPA Pyelonephritis definition: Bacteriuria and fever of ≥38.5°C and a microsedimentation rate of ≥25mm per hour or CRP ≥20mg/L Cystitis definition: acute voiding symptoms (dysuria, frequency) with temperature <38.5°C and normal laboratory findings. A child with acute symptoms and bacteriuria that could not be classified was said to have 'unspecified UTI'	Outcome measures: No. with reflux (and grade) No. with scarring No. of symptomatic recurrences No. with pyelonephritis/cystitis	Study 1 225/1177 (19%) boys 952/1177 (81%) girls <u>Boys</u> 133/225 (59%) of UTIs detected in the first year of life 72/225 (33%) had VUR 8/72 (11%) dilated reflux (grade ≥3) 41/225 (18%) had one recurrence 11/225 (5%) had 2 or more recurrences <u>Girls</u> 181/952 (19%) of UTIs detected in the first year of life 315/952 (34%) had VUR (54% between 1-3 years) 25/315 (8%) dilated reflux (grade ≥3) 152/952 (16%) had one recurrence 152/952 (16%) had 2 or more recurrences <u>Scarring</u> 15/278 (5%) children with no reflux had scarring 3/29 (10%) of children with grade 1 reflux had scarring 17/99 (17%) of children with grade 2 reflux had scarring	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
						25/38 (66%) children with grade ≥3 reflux had scarring 25% of the total number of children with scarring did not have reflux. <u>Pyelonephritis</u> 7/141 (5%) children with 0 pyelonephritis episode had scarring 32/366 (9%) of children with 1 pyelonephritis episode had scarring 15/98 (15%) of children with 2 pyelonephritis episode had scarring 12/35 (35%) of children with 3 pyelonephritis episode had scarring 14/24 (58%) children with ≥4 pyelonephritis episode had scarring	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Zorc JJ;Levine DA;Platt SL;Dayan PS;Macias CG;Krief W;Schor J;Bank D;Shaw KN;Kupperma nn N; 2005 [107]	Study Type: Cross-sectional Evidence Level: 3	To identify clinical and demographic factors associated with UTI in febrile infants who are ≤60 days old.	1025 infants	Infants aged from 1 to 60 days (mean 35.5 ± 14.4 days) UTi was defined as growth of a known bacterial pathogen from a catheterised sample at ≥50000cfu/ml or ≥10000cfu/ml in association with a positive dipstick test or urinalysis.	Outcome measures Age ≤28 days Gender Circumcision Ill appearance (YOS>10) Height of fever White race	Factor present, Factor absent, OR (95%CI) Uncircumcised (vs. circumcised male), 62/291vs. 6/262, OR 11.6 (5.0 to 26.6) Max temperature >39°C (vs. <39), 34/209 vs. 57/796, OR2.5 (1.6 to 4.0) Female (vs. circumcised male), 22/439 vs. 6/262, OR 2.2 (0.9 to 5.5) Age <28 days (vs>28 days), 37/334 vs. 54/671, OR 1.4 (0.9 t 2.2) Ill appearing (YOS>10), 4/71 vs. 87/924, OR .6 (0.2 to 1.6) White (vs. other race), 12/259 vs. 79/44, OR 0.4 (0.2 to 0.8) Adjusted OR (Bias-corrected 95%CI) p-value Uncircumcised: 10.4 (4.7 to 31.4) p<0.001 Maximum temperature: 2.4 (1.5 to 3.6) p<0.001 Female: 2.2 (0.9 to 6.6) p=0.10 Age <28 days: 1.6 (0.96 to 2.6) p=0.07 Ill appearing: 0.68 (0.14 to 1.6) p=0.49 White: 0.79 (0.35 to 1.5) p=0.53	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Falcao MC;Leone CR;D'Andrea RA;Berardi R;Ono NA;Vaz FA; 2000 Jan [108]	Study Type: x-sectional. Evidence Level: 3	To analyse the contribution of risk factors to the occurrence of urinary tract infection in full term newborn infants.	61 infants (26 boys, 35 girls).	Infants (gestational age 37 to 42 weeks) presenting with fever (>37.8ºC), weight loss (>10% of birth weight) or non-specific symptoms (feeding intolerance, failure to thrive, hypoactivity, debilitate suction, irritability). In these children another urine sample was collected by SPA to confirm diagnosis. Group I: positive urine culture by urine collection bag, negative on SPA Group II: positive urine culture by urine collection	Associated infectious pathologies, use of broad spectrum antibiotics, renal and urinary tract malformations, mechanical ventilation, parenteral nutrition and intravenous catheter.	On SPA, 42 infants were culture negative (group I) and a diagnosis of UTI was confirmed in 19 (group II). There were no significant differences between groups for birth weight, sex, asphyxia or membrane rupture time. On presentation there were no differences between the groups for fever (p=0.31), however there were significant differences for weight loss (>10% of birth weight) (p=0.01) and non-specific symptoms (p=0.0004) Group 1 vs. Group 2 (p-value) Birth weight 3399.52 (±418.36) vs. 3171.05 (±515.08) (p=0.07) Sex	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
				bag, positive on SPA Definition of positive urine sample was 10^5cfu/ml of a single organism for bag collection and any growth on SPA.		Male - 16 (38%) vs. 10 (53%) (p=0.28) Female - 26 (62%) vs. 9 (47%) (p=0.28) Asphyxia (Apgar 5'<6) 1 (2.4%) vs. 3 (15.8%) p=0.14 Membrane rupture time ≥24 hours 7 (17%) vs. 5 (26%) p=0.47 Fever (>37.8ºC) 38 (91%) vs. 15 (79%) p=0.31 Weight loss >10% of birth weight 20 (48%) vs. 3 (16%) p=0.01 Nonspecific symptoms 4 (9.5%) vs. 10 (53%) p=0.0004 Risk factors	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
						Associated infectious diseases 9 (21%) vs. 12 (63%) p=0.001 RR 3.27 (95%CI 1.51 to 7.04) p=0.0001 Use of broad-spectrum antibiotics 3 (7%) vs. 6 (32%) p=0.02 RR 3.03 (95%CI 1.51 to 6.08) p=0.012 Renal and urinary tract malformations 4 (9.5%) vs. 7 (37%) p=0.01 RR 2.97 (95%CI 1.57 to 5.64) p=0.007 Mechanical ventilation 1 (2%) vs. 4 (21%) p=0.04 RR 2.99 (95%CI 1.61 to 5.53) p=0.029 Parenteral nutrition 1 (2%) vs. 10 (53%) p=0.0006	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
						RR 5.05 (95%CI 2.72 to 9.39) p=0.0009 Intravascular catheter 1 (2%) vs. 5 (26%) p=0.01 RR 3.27 (95%CI 1.84 to 5.83) p=0.009	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Go JMR;Cocjin A;Dee-Chan R; 2005 [109]	Study Type: Case-series Evidence Level: 3	To determine if unexplained and/or excessive jaundice is associated with UTI in infants aged less than 8 weeks of age.	54 infants (22 boys, 32 girls)	All jaundiced , full term (37-42 weeks gestation) infants less than 8 weeks old, born between October 2002 and October 2004. Clinical jaundice was defined as yellowish discolouration of the skin, mucous membranes or sclera. Exclusions: Infants who had previously been evaluated for sepsis and who were treated with intravenous antibiotics, minor infections where jaundice was caused by other known factors.	Detailed questionnaires on prenatal, intrapartum and post-natal events were completed WBC count Serum fractioned bilirubin levels Urinalysis Blood and urine culture	150 infants were born over a two year period, of which 73 presented with jaundice. 19 cases were excluded, 16 because of ABO incompatibility, 2 because of pneumonia and one because of cephalhematoma. Of the 54 included infants, 5 had UTI and 49 did not. Historical and demographic characteristics Gender (p>0.05) Age (p>0.05) Place of birth (p>0.05) Mode of delivery (p>0.05) Birth weight (p>0.05) Gestational age (p>0.05) Stay at nursery (p>0.05) Neonatal infection (p>0.05) Mixed feeding Onset of jaundice (p>0.05) Progression Maternal characteristics: Maternal age (p>0.05) Gravidity (p>0.05) Presence of maternal infection (p>0.05) Maternal illness (p>0.05) Infants with UTI vs. infants without UTI, p-value	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
						Total bilirubin – 13.38 ± 1.40 vs. 8.91 ± 2.11, p<0.001 Direct bilirubin – 1.38 ± 1.22 vs. 0.28 ± 0.16, p<0.01 Indirect bilirubin – 11.96 ± 1.32 vs. 8.91 ± 2.11, p<0.01	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Hiraoka M;Tsukahara H;Ohshima Y;Mayumi M; 2002 [110]	Study Type: Case control Evidence level: 2-	Distribution of phimosis in boys with first episode of febrile UTI compared with 'healthy' control boys, and male to female ratio of febrile UTI by age and sex.	100 children with febrile UTI (64 boys and 36 girls) and 714 healthy boys	Cases: consecutive children who presented at one hospital with febrile UTI from July 1995 to May 2000 febrile UTI defined as: body temp above 38.5C, ≥50,000 cfu/ml for catheterized urine, one strain, or $\geq 10^5$ cfu/ml for midstream or clean-catch urine Controls: 'healthy' boys, aged 0-3 yrs, uncircumcised. Recruited either at birth or during a health check-up at the same hospital	male:female ratio of first time febrile UTI. Proportion of boys with P0 (external urethral meatus not naturally covered with the prepuce), P1 (prepuce covers external meatus and is fully retractable), P2 (prepuce covers meatus but is only partially retractable), P3 (prepuce covers meatus but retraction does not allow exposure of meatus), or P4 (prepuce covers meatus and is not retractable at all)	From 100 children with febrile UTI, first time infection in 58 boys and 20 girls under age of 7 months male:female ratio of febrile UTI = 5.0; at 1 yr or more ratio = 0.10 85% of boys with febrile UTI under age of 7 months (n=55) had prepuce state P3 or P4; approx 42% of 'healthy' boys under age of 7 months had prepuce state P3 or P4; OR 7.8 (95% CI 3.99 to 15.31)	Unclear why author's chose to report distribution of phimosis only in boys with febrile UTI under 7 months of age Also unclear why author's excluded children between 7 and 11 months old when reporting male:female ratios for first time febrile UTI 95% CI not reported (calculated at NCC-WCH)

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Jerkins GR;Noe HN; 1982 Oct [111]	Study Type: Case-series Evidence Level: 3	To identify a group at risk for VUR using awake voiding cystogram	n=104 siblings of patients with VUR (67 female, 37 male)	Siblings were from 78 white patients (60 female and 18 male) with VUR (regardless of UTI history) and were aged 3 months to 15 years	No. of siblings with VUR No. of siblings with VUR by age group No. with VUR with history of UTI	34/104 (32.7%) sibs (25 female (37.3%), 9 (24.3%) male) found to have VUR 16/49 (32.7%) sibs aged 0 to 3 years had VUR 9/23 (39.1%) sibs aged 4-6 years had VUR 9/32 (28.1%) sibs aged 7 years or older had VUR Of 34 with VUR, 6 (17.6%) had history of UTI and 25 (73.5%) had no history of UTI	Impossible to make such a conclusion without context of a comparison group, i.e., these siblings are at much higher risk than who? Among 34 with VUR, 31 had either a history or no history of UTI. Although the remaining 3 patients had a history of abnormal voiding patterns, it was unclear why their UTI status was ignored. Would also be useful to know how many in group without VUR had history of UTI for comparison. No. of siblings with unilateral and bilateral VUR not reported.

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Ataei N;Madani A;Esfahani ST;Kejbafzadeh A;Ghaderi O;Jalili S;Sharafi B; 2004 [112]	Study Type: Case-series Evidence Level: 3	To assess number of VUR cases in siblings of patients with VUR by voiding cystourethrogram (VCUG)	40 siblings (25 female, 15 male) of patients with VUR	Siblings were from 34 patients with VUR (irrespective of history of UTI) and ranged from 6 months to 12 years in age. Sibs were screened from Oct 1994 to Feb 2003	No. sibs with VUR No. of VUR with history of UTI	17/40 (42.5%) sibs with VUR Of 17 with VUR, 5 (29.4%) had history of symptomatic UTI bilateral in 6/17 and unilateral in 11/17 siblings	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Singh-Grewal D;Macdessi J;Craig J; 2005 [113]	Study Type: Systematic review / meta-analysis Evidence Level: 2++	To undertake a meta-analysis of published data on the effect of circumcision on the risk of UTI in boys.	Data on 402,908 boys were identified from 12 studies.	Boys of any age where the intervention was circumcision and UTI was the outcome. Only studies that provided a 2x2 table were included so that odds of UTI could be calculated.	Outcome: UTI	RCT – One RCT had an OR of 0.13 (95%CI 0.01 to 2.63) Cohort studies – All four cohort studies showed benefit with a summary OR of 0.13 (95%CI 0.07 to 0.23), however there was significant heterogeneity between studies (x^2 = 82.48, df = 3, p<0.001). When the one outlying study was excluded, the heterogeneity was not significant (p=0.64) Case-control – All 7 case-control studies included showed benefit with a combined OR of 0.13 (95%CI 0.07 to 0.23). There was no significant heterogeneity between studies (x^2 = 8.15, df = 6, p = 0.2) All studies – The summary OR across all study types was 0.13 (95%CI 0.08 to 0.20). There was no significant heterogeneity observed between study types (x^2 = 0.16, df = 2, p = 0.9), however significant heterogeneity was observed the individual studies (x^2 = 90.63, df = 11, p<0.0001) owing to the inclusion of the cohort studies. Without this study there was no	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
						significant heterogeneity (x^2 = 10.92, df = 10, p<0.4). The odds of a circumcised boy having a UTI are about 0.1 when compared with uncircumcised boys. While circumcision is shown to be protective against UTI, the risk-benefit of circumcision is not easily quantifiable. The study concludes that while circumcision substantially reduces the risk of UTI, routine circumcision should not be considered. Circumcision has a potential role in boys with past history of recurrent UTI, or with high grade VUR, as the benefits in these cases may outweigh the risk of complications	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Schoen EJ; Colby CJ;Ray GT; 2000 Apr [114]	Study Type: Cohort Evidence level: 2++	Effect of circumcision, performed before discharge after birth or during newborn period, on UTI	1996 cohort: n= 28,812 infants 1997 cohort (for incidence study): n= 20,587 infants	All children born at 12 facilities that were a part of the Kaiser Permanente Medical Care Program of Northern California; n=14,893 were male infants in the 1996 cohort	Follow-up period: For 1997 incidence study, 12 months. Outcome Measures: Number circumcised (%) Number of UTI before 1 year Median age at hospitalisation for UTI Incidence of UTI	Of 14,893 male infants born in 1996, 9668 (64.9%) were circumcised In 1996, 446 UTI cases were diagnosed (292 female, 154 male) in infants <1yr old Median age at diagnosis was 2.5 months for uncircumcised male, 4.5 months for circumcised male, and 6.5 months for female infants Incidence of UTI in first year of life 1:47 for uncircumcised male, 1:455 for circumcised male, and 1:49 for female infants; OR for uncircumcised compared with circumcised = 9.1 (95% CI 5.2 to 15.7)	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Wiswell TE;Geschke DW; 1989 Jun [115]	Study Type: Cohort Evidence level: 2+	Retrospective review of hospital records for complications related to circumcision status in first month of life.	136,086 boys	All boys born in US army hospitals from Jan 1980 to Dec 1985	No. circumcised No. of complications in first month of life No. of UTI; association between UTI and circumcision by chi square	100,157 (73.6%) circumcised; 35,929 (26.4%) uncircumcised 193 (0.19%) complications in 193 circumcised boys, including 20 UTI, 5 concomitant cases of bacteremia, 83 haemorrhage, 0 deaths 88 (0.24%) complications in 88 uncircumcised boys, all UTI, 32 concomitant cases of bacteremia, 2 deaths association between UTI and circumcision significant at p<0.0001	Results may be an underestimate of actual frequency of adverse sequelae in both circumcised and uncircumcised boys; minor complications may not have been indexed in records, lesser problems may have been treated on outpatient basis, some children may have been admitted to civilian hospitals No chi square value reported

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Wiswell TE;Smith FR;Bass JW; 1985 [116]	Study Type: Cohort Evidence level: 2+	Records of infants who were hospitalised during the first year of life for UTI were reviewed to document incidence of UTI in first year of life	5261 infants (2759 female, 2502 male)	Medical records of all infants born between 1982 and 1983 at an army medical centre. UTI defined as $\geq 10^5$ cfu/ml, one strain, by SPA or catheter	No. evaluated for UTI No. with diagnosed UTI No. males circumcised Mean age at time of diagnosis Associations tested using chi square	400/5261 (7.6%) infants evaluated for UTI 41/5261 (0.78%) infants diagnosed with UTI: 13 female 4 circumcised male 24 uncircumcised male incidence of UTI in males higher than in female ($p<0.01$) incidence of UTI in uncircumcised higher than in circumcised ($p<0.001$) 1919/2502 (76.7%) males circumcised female age: 2.5 mo circumcised male: 1.4 mo uncircumcised male: 1.7 mo age range: 10 days to 11 months; 34/41 (83%) were <3mo	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Wisell TE;Enzenauer RW;Holton ME;Cornish JD;Hankins CT; 1987 [117]	Study Type: Cohort. Evidence level: 2+	Records of infants who were hospitalised during the first year of life for UTI were reviewed to document incidence of UTI in first year of life	427698 infants (207923 female, 219775 male)	All infants born between 1975 and 1984 in US army hospitals UTI defined as ≥ 10^5 cfu/ml, one strain, by SPA or catheter.	No. of UTI by gender No. males circumcised No. of UTI by circumcision status	Females: 1051/207923 (0.51%) with UTI, males: 610/219775 (0.28%) with UTI; chi square = 143.5, p<0.001 173663/219775 (79%) males circumcised UTI in circumcised: 151/173663 (0.09%), UTI in uncircumcised: 459/46112 (99.5%); chi square = 1086.43, p< 0.001	Chi square and p-value calculated by NCC-WCH

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
To T;Agha M;Dick PT;Feldman W; 1998 Dec 5 [118]	Study Type: Cohort Evidence level: 2++	Circumcision and subsequent risk of UTI (defined by ICD-9 codes for infections of the kidneys, cystitis, urethritis, other unspecified UTI)	Hospital discharge data on 69,100 boys	Born to residents of Ontario between 1 April 1993 and 31 March 1994; n=30,105 circumcised within first month of life, n=38,995	Follow-up period: From birth until first UTI or until 31 March 1996. Outcome Measures: Hospital admission for UTI during the 2-3 years of follow-up NNT	1 month probability of hospital admission for UTI (per 1000 person-yrs): 0.34 for circumcised and 1.54 for uncircumcised; relative risk 4.5, 95% CI 2.4 to 8.4 1 year probability of hospital admission for UTI (per 1000 person-yrs): 1.88 for circumcised and 7.02 for uncircumcised; relative risk 3.7, 95% CI 2.8 to 4.9; 195 circumcisions needed to prevent 1 hospital admission for UTI in first year of life 3 year probability of hospital admission for UTI (per 1000 person-yrs): 2.96 for circumcised and 8.75 for uncircumcised; relative risk 3.0, 95% CI 2.4 to 3.8	

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Craig JC;Knight JF;Sureshkumar P;Mantz E;Roy LP; 1996 [119]	Study Type: Case-control Evidence level: 2+	The association between circumcision and risk of UTI and whether this association is independent of age	n=144 circumcised boys with UTI and n=742 controls	Cases: boys, aged <5 years, presenting with symptomatic UTI, with no previous history of diagnosed UTI, from pediatric department of children's hospital from Mar 1993 to Dec 1994 UTI defined as: for SPA or catheter, growth >10^6 cfu/L, one strain; for midstream, >10^8 cfu/L, one strain; PLUS, symptoms and/or signs of UTI Controls: all boys, aged <5 years, without UTI, presenting at the same department in the same hospital as the case boys for one month (Apr) in 1995	No. circumcised, chi square Median age, Mann-Whitney U Association between circumcision and UTI by age, chi square and odds ratio Breslow-Day test for homogeneity	47/742 (6.3%) controls circumcised, 2/144 (1.4%) cases circumcised; chi square = 5.6, p=0.02 median age = 21 months for controls, 5.8 months in cases; p<0.001 under 1 yr: chi square = 3.9, p=0.05; OR 0.3, 95% CI 0.06 to 1.1 1 yr and older: chi square = 2.2, p=0.1; OR 0.2, 95% CI 0.01 to 3.7 combined OR (mantel-haenszel) = 1.8 , 95% CI 0.05 to 0.70; homogeneity, p = 0.4	Statistics vary from what is calculated by NCC-WCH on STATA using numbers provided in paper, e.g. one set of 95% CI presented in paper did not include the OR and was recalculated at NCC-WCH Study did not confirm that controls had no UTI using microbiology

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Herzog LW; 1989 [120]	Study Type: Case-control Evidence level: 2+	Association between UTI and circumcision in boys aged < 1year and investigation of whether ethnic, racial or socio-economic factors play a role	n=36 boys with UTI and n=76 controls	From all 211 boys <1 yr old who had urine culture done in ER at one children's hospital for 1985 and 1986, cases were those who had SPA or catheter yielding $>10^5$ cfu/ml, one strain Controls were patients with negative SPA or catheter culture, i.e., <1000 organisms/ml Infants whose circumcision status could not be determined (n=1 case and n=29 controls), those whose race could not be determined (n=13 controls), those with previous UTI anatomic problems or equivocal results (n=59) were excluded	No. circumcised Mean age Differences in circumcision by age, race, and type of insurance	0/36 cases circumcised, 52/76 (68%) controls circumcised; p<0.0001 3.7 months for cases, 4.5 months for controls; p not significant Also no differences between cases and controls in ethnic group or type of medical insurance Cases less likely to be circumcised if <3mo (p<0.0001) and if >3mo (p<0.0001) Cases less likely to be circumcised among Hispanics (p=0.02), blacks (p<0.001) and whites (p=0.0003) cases less likely to be circumcised for all types of insurance (all p ≤ 0.01)	Abstract mentions no significant difference between cases and controls by ethnic group but this result is not reported in the results section of the paper. Note small sample size.

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Marild S;Hansson S;Jodal U;Oden A;Svedberg K; 2004 Feb [121]	Study Type: Case-control Evidence level: 2+	Association between breastfeeding and the risk of first time febrile UTI and the dose-response of protective effect of duration of breastfeeding assessed by interview and questionnaire	n= 200 consecutive children with UTI (89 male, 111 female) and n=336 controls (147 male, 189 female)	Cases: children age 0-6 yrs presenting with first-time symptomatic UTI in two paediatric departments Inclusion criteria: fever of >38.4°C within 24 hr of diagnosis plus bacteriuria; bacteriuria defined as one of the following: for SPA, growth of any cfu/ml, one strain; for midstream samples, growth ≥10^5 cfu/ml, one strain; for bag urine, two separate specimens with growth ≥10^5 cfu/ml, same strain in both specimens. Controls: aimed for 2 per case, enrolled consecutively; no history of previous UTI or urinary tract anomalies; matched for gender and age and registered at same hospital of case.	Duration of exclusive breastfeeding at time of interview Risk of UTI when breastfed v. not breast fed, difference in risk of UTI between girls and boys, and risk of UTI in relation to duration of breastfeeding assessed by Poisson regression risk of UTI in first two years of life after weaning	Mean duration of breastfeeding (wks± SD): girl cases: 16±9.2 girl controls: 18±9.2 boy cases: 11±8.9 boy controls: 12±8.4 Non-breastfed compared with breastfed: Overall: risk of UTI increased 2.3 times (95% CI 1.56 to 3.39) Girls: risk of UTI increased 3.78 times Boys: risk of UTI increased 1.63 times Longer duration of exclusive breastfeeding significantly reduced probability of UTI; the protective effect of exclusive breastfeeding was strongest right after birth for girls and then decreased until 7 months. In boys, protective effect was less marked and constantly decreased as age increased. Risk of UTI increased rapidly if breastfeeding discontinued after 2 months; lower risks of UTI were observed with weaning after 7 months breastfeeding.	Confidence intervals for all results not provided, in particular, provided for overall, but not individual groups No measures to control for recall bias mentioned in the study methods Study did not confirm that controls had no UTI using microbiology

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Nuutinen M;Huttunen N;Uhari M; 1996 [122]	Study Type: Case-control Evidence level: 2+	Risk of contracting UTI according to different nappy types used prior to first UTI diagnosis	n = 196 children with UTI (104 female, 92 male) and n=196 controls (104 female, 92 male)	Cases: children who were 'nappy age' and used nappies day and night presenting with first UTI in one of 2 children's hospitals from 1987 to 1994 Inclusion criteria: for SPA, growth of any cfu/ml; for two subsequent clean voided urine samples, growth ≥10^5 cfu/ml, same strain in both specimens. Controls: children who were hospitalised for some other reason, matched for gender and age	Outcome Measures: Odds of UTI	Disposable: 0.95, 95% CI 0.62 to 1.46 super absorbent: 1.04, 95% CI 0.69 to 1.57 washable cotton: 1.00, 95% CI 0.46 to 2.16 No significant differences in nappy habits were reported (including daily number of nappies used, number of defecations per day, frequency of buttock washes, daily time spent without a nappy, and occurrence of nappy rash)	Study did not confirm that controls had no UTI using microbiology - although this does not affect the study outcome as the null hypothesis was not rejected. No measures to control for recall bias mentioned in the study methods

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Hoi LV;Sarol JN;Uriarte RD;Tadoy SA; 2000 [123]	Study Type: Case-control Evidence level: 2-	Face-to-face interviews, validated by interview with parents	n =23 children with UTI and n=23 controls; 60.9% female, 39.1% male	Cases: out-patient children aged 6-12 (mean 8.63yrs) with UTI from 4 tertiary hospitals from Sept 1998 to Sept 1999 UTI determined by: for midstream urine, growth of at least 10^5 cfu/ml, one strain, or medium to high growth as identified by aerobic method Controls: selected soon after case was identified, included children presenting with any disease or condition other than urinary diseases and selected hygiene-related diseases	Outcome Measures: Previous history of UTI Increased risk of UTI associated with urination, defecation, washing and bathing habits Association between UTI and age group, school enrolment history of UTI, presence of preschooler in the same household and holding of urination examined in multivariate analysis	21.7% of cases had previous history of UTI compared with 4.3% of controls No increased risk of UTI was observed for bathing habits (daily v. less than daily), urinary frequency (less than 5 times/day or 5+ per day), holding urine during the day (yes or no), permission to urinate at school (during break v. whenever), washing after urination (yes or no), washing after defecation (yes or no), direction of washing (from behind v. from front), or use of soap during washing (yes or no) In multivariate analysis: Adjusted OR 6.18 (95% CI 1.04 to 54.60) for age group and 5.78 (95% CI 1.01 to 51.02) for school enrollment; all other variables NS	Did not specify whether controls were matched for age and gender Did not specify if controls were selected from the same hospital as case Number excluded or declined to participate not specified Small sample size resulted in wide confidence intervals Study did not confirm that controls had no UTI using microbiology No measures to control for recall bias mentioned in the study methods

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
Hansen A;Hansen B;Dahm TL; 1997 [124]	Study Type: x-sectional. Evidence Level: 3	Questionnaires to investigate the potential correlation between UTI and voiding habits (denominators vary due to incomplete questionnaires)	1557 children (823 female, 728 male, 6 without gender identification)	1557/2780 (56%) questionnaires from children aged 6 to 9 years old from 77 schools.	No. reporting previous UTI No. reporting more than one previous UTI Frequency of micturation Micturation habits compared by chi-square for females only (number of boys too small)	75/823 (9.1%) girls and 20/728 (2.7%) boys reported previous UTI 27/75 (36%) girls and 4/20 (20%) had had more than one previous UTI. No significant difference in frequency of micturation between children with and without prior history of UTI (median number voidings for all children = 5/day) <u>Signs and symptoms</u> Micturation habits in previous UTI v. no UTI: bed wetting, 19/75 v. 90/723, p = 0.002 day wetting, 22/75 v. 93/723, p <0.0002 does not reach toilet, 30/75 v. 202/723, p=0.03 prolonged voiding, 25/75 v. 129/723, p<0.002 poor stream, 22/75 v. 114/723, p<0.003 staccato voiding, 23/75 v. 126/723, p<0.006 able to void again, 24/75 v. 1252/723, p<0.002 straining, 13/75 v. 62/723, p=0.02 manual compression of	Major limitation of study is the low response rate: 56% Study design subject to recall bias, e.g., inflated numbers due to parents of children with wetting problems being more likely to respond. Statistical test for frequency of micturation not reported.

Bibliographic Information	Study Type & Evidence Level	Aims and comparisons	Number of Patients	Patient characteristics	Follow-up & Outcome Measures	Effect Size	Reviewer comment
						abdomen, 13/75 v. 53/723, p<0.003 encopresis, 10/75 v. 43/723, p=0.03	

1

1 **Symptoms and signs**

2

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
Craig JC;Irwig LM;Knight JF;Sureshkumar P;Roy LP; 1998 Apr [125]	Study Type: Case-series Evidence Level: 3	To describe the demographic and clinical features of children with symptomatic UTI	n=305 children (169 male, 135 female) with UTI	Children aged <5 years presenting consecutively at the emergency hospital of a children's hospital with first documented symptomatic UTI from 1993 to 1994 UTI defined as: for SPA or catheter, $>10^6$cfu/L, one or two strains; for midstream urine > 10^7 cfu/L, one or two strains; for bag urine, $>10^8$ cfu/Land urinary white cell count >100 x 10^6/L	Age and gender of children with UTI Frequency of clinical features of children presenting with UTI	Males (n=169) with UTI: 0 to 1 yr: 127 (75.1%) 1 to 2 yrs: 13 (7.7%) 2 to 3 yrs: 12 (7.1%) 3 to 4 yrs: 7 (4.1%) 4 to 5 yrs: 10 (5.9%) Females (n=135) with UTI: 0 to 1 yr: 68 (50.3%) 1 to 2 yrs: 26 (19.3%) 2 to 3 yrs: 19 (14.1%) 3 to 4 yrs: 15 (11.1%) 4 to 5 yrs: 7 (5.2%) Symptoms (from n=304): History of fever, 242 (79.6%) Axillary temp >37.5, 181 (59.5%) Irritability, 159 (52.3%) Anorexia, 148 (48.7%) Malaise/lethargy, 135, (44.4%) Vomiting, 127 (41.8%) Diarrhoea, 63 (20.7%) Dysuria, 45 (14.8%) Offensive urine, 40 (13.2%) Abdominal pain, 40 (13.2%) Frequency, 29 (9.5%) Macroscopic haematuria, 20 (6.6%)	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
Ginsburg CM;McCracken GH; 1982 Apr [104]	Study Type: Csae-series Evidence Level: 3	To present clinical and laboratory features of UTI	100 infants 62 boys 38 girls	Infants aged 5 days to 8 months (mean 2.1 months) admitted to one of two hospitals with acute UTI from Mar 1976 to Feb 1981	Frequency of signs and symptoms	<u>Age distribution</u> Male infants accounted for 75% of UTI cases within the first three months of life compared with 11% of boys who were 3 to 8 months of age. Of the 41 infants who were under 30 days old, 33 (81%) were boys. <u>Signs and Symptoms</u> Fever was the most common symptom (in 63%) and symptoms of irritability (55%), had refused feeds (38%), vomiting (36%) and diarrhoea (31%). 67 infants had a fever of ≥38°C and 38 infants had fever of ≥39°C. Abdominal distention and jaundice were only reported in 8% and 7% of patients respectively.	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
Burbige KA;Retik AB;Colodny AH; 1984 [126]	Study Type: Case-series Evidence Level: 3	To present clinical and laboratory features of UTI	83 boys	Boys aged 2 weeks to 14 years treated at a children's hospital with first time UTI. (mean age unknown) UTI defined as >100,000 cfu/ml.	Age and gender of children with UTI Frequency of clinical features of children presenting with UTI Frequency of signs and symptoms	<u>Age distribution</u> Of the 83 boys, 25% were ≤1 year old and half were < 6 years old. The incidence of urinary tract abnormalities was distributed evenly through the group. <u>Symptoms</u> Fever 40/83 (48%) and the only presenting sign in 25%. Irritative bladder syndromes 23/83 (28%) Abdominal or flank mass 11/83 (13%) Enuresis 7/83 (8%) Gross haematuria 6/83 (7%)	No definition of fever

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
Pennesi M;Salvatore CM;Peratoner L; 1998 Dec [127]	Study Type: Cross-sectional Evidence level: 3	Questionnaires to determine which clinical factors at presentation can be used to determine whether or not to perform MCUG	227 children (142 female, 85 male) with acute pyelonephritis.	Children, aged 15 days to 4 yrs, admitted to one of 9 paediatric departments at first episode of acute pyelonephritis.	Outcome Measures: No. with fever (>=38.5C) No. with symptoms preceding onset of fever (including low fever, anorexia, irritability or drowsiness, diarrhoea, foul-smelling urine) No. with VUR (by MCUG)	92/227 (40.5%) with VUR 218/227 (96%) with fever 114/218 (52.3%) with symptoms before onset of fever 16/114 (14.0%) with symptoms before fever had VUR 85/104 (81.7%) without symptoms before fever had VUR	Study published as a letter

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
Messi G;Peratoner L;Paduano L;Marchi AG; 1988 [40]	Study Type: Case-series Evidence Level: 3	To present clinical and laboratory features of UTI and to determine incidence of UTI	223 children (38 males, 185 females)	Children aged 0-14 years presenting with symptomatic UTI and treated at a hospital. UTI was defined as two consecutive urine cultures yielding $>10^5$cfu/ml of the same bacteria and microscopic examination yielding more then 10leukocytes/mm^3	Presenting symptoms Number with UTI Number with cystitis Number with pyelonephritis Number with VUR Renal scarring Urinary tract malformations	64/223 (29%) aged >1 year 63/223 (28%) aged 1-4 years 96/223 (43%) aged 5-14 years <u>Signs and symptoms</u> Fever 144/223 (64.6%) Dysuria and frequency 92/223 (41.2%) Gastrointestinal symptoms 42/223 (18.8%) Haematuria 24/223 (10.8%) Failure to thrive 14/223 (6.3%) Jaundice 2/223 (0.9%)	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
Smellie JM;Ransley PG;Normand IC;Prescod N;Edwards D; 1985 Jun 29 21	Study Type: OtherCase-series Evidence Level: 3	Factors surrounding the development of renal scars	120 children	Children aged 2 weeks to 12 years who had an intravenous urograms and a UTI seen between 1960 and 1982. New scars were defined as the development of a caliceal deformity with thinning of the overlying renal parenchyma in an area of kidney considered to be normal in the previous urogram. Exclusions: solitary, duplex or horseshoe kidneys, kidney stones, mechanical or neuropathic or postoperative obstruction. Definition of UTI not reported.		Scars developed in 87 kidneys of 74 children (8 boys, 66 girls) New scars 58/74 (78%) of children had normal kidneys initially; unilateral scarring in 46, bilateral in 12 Progressive scars 13/74 (18%) had unilateral scarring initially and developed additional scars 3/74 children had bilateral scarring initially and developed additional scars All children with scarring had UTI 61/74 (82%) due to E. coli. Presenting symptoms: fever (57/74) 77% abdominal or loin pain (34/74) 46% chronic constipation (16/74) 21% uncoordinated voiding with residual urine (8/74) 11% 67/74 (91%) children had reflux, new scars developed with all grades of reflux. However there was a greater tendency for scaring to occur in more severe reflux. 51% of the children who	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
						developed scarring had previously had a UTI.	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
Honkinen O;Jahnukainen T;Mertsola J;Eskola J;Ruuskanen O; 2000 Jul [42]	Study Type: Case-series - population surveillance data Evidence Level: 3	To assess the clinical characteristics of bacteremic UTI in children.	134 children (82 girls, 52 boys) located from all 36 Finish hospitals and 25 microbiological laboratories, between 1985 and 1994 Comparison group 134 age and sex matched from children hospitalised for blood culture negative symptomatic UTI	Children aged 7 days to 9.5 years (median 0.125 years) with serious bacteremic UTI. Inclusion criteria were symptoms of acute illness such as fever, irritability, vomiting or dysuria; bacterial growth $\geq 10^5$ in one midstream urine or in two urine bag samples; growth of identical pathogen both in the blood and in the urine cultures; first known urinary tract infection; and no known urinary tract abnormality or other severe underlying disease. 29 children had a history of UTI or urinary tract abnormality or other severe underlying disease. 7 children were under 1 week old and analysed separately	Age and sex distribution of bacteremic UTI Signs and symptoms Laboratory findings Microbiological findings	<u>Age distribution</u>: 89/134 (66%) 1 week - 3 months; 61/89 (69%) of youngest age group were boys) 30/134 (22%) 3 to 11 months 16/134 (12%) ≥ 12 months <u>Signs and symptoms</u>: No. with Bacteraemic UTI (%) v No. with Nonbacteraemic UTI (%) Fever 124 (92%) v 121 (90%) Irritability 81 (60%) v 75 (56%) Abnormal crying 46 (34%) v 41 (30%) Vomiting 22 (16%) v 18 (13%) Lethargy 35 (26%)v 41 (30%) Feeding problems 27 (20%) v 13 (10%) Abdominal pain 10 (7%) v 4 (3%) Dysuria 2 (1%) v 4 (3%) Convulsions 5 (4%) v 0 (0%) Only feeding problems were reported more often in bacteremic patients (20% vs. 10 %, p = 0.02). The duration of the preceding fever showed no difference between the two study groups (mean, 1.9 ± 1.9 vs. 1.8 ± 1.7	Some of the Children included in this study may have been included in the study Ref ID 1068

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
						days, respectively). In patients ≥ 12 months old (n = 17), fever had lasted 2.7 ± 2.1 days in non-bacteremic patients vs. 1.7 ± 1.5 days in bacteremic patients (p = 0.11). No difference was found in the mean values for the highest temperature on admission (39.4 ± 0.5 vs. 39.1 ± 0.5ºC). Two of the patients in both study groups were afebrile (body temp. < 38.0ºC).	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
Nayir A; 2001 Dec [128]	Study Type: RCT Evidence Level: 3	To present clinical characteristics of UTI and to determine whether circumcision decreases the risk of significant bacteriuria and prevents recurrence. By patient interview.	88 boys	Boys aged 3 months to 10 years (mean age 30.3 months ± 26.6 months) with first time symptomatic UTI referred to a paediatric nephrology department. Boys with existing uropathies were excluded. Bacteriuria defined as growth of a single urinary pathogen at 10^5cfu/ml. Urine was collected by bag in 47/88 (53%) of boys and by mid-stream in 41/88 (47%)	Age distribution of UTI Signs and symptoms	Age distribution 47/88 (53%) aged >2 years 23/88 (26%) aged 2-5 years 18/88 (20%) aged <5 years <u>Signs and Symptoms</u> Fever <38.5°C 42 (48%) Fever >38.5°C 21 (24%) Vomiting and/or diarrhea 19 (22%) Dysuria/frequency 30 (34%) Enuresis 6 (7%) Suprapubic discomfort 10 (11%) Abdominal pain 16 (18%) Flank pain 4 (5%) Malodorous urine 2 (2%)	Only presenting symptoms of this RCT presented here. See recurrence evidence tables for full review.

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
Smellie JM;Normand IC;Katz G; 1981 [51]	Study Type: Case-series Evidence Level: 3	To examine the clinical features of children presenting with UTI to determine whether there were any differences between those with and those without VUR	744 children, 179 boys and 565 girls	Children aged 0 to 12 years treated in a paediatric department with bacteriologically proven UTI. All children were investigated with intravenous urography (IVU) and MCUG.	Age distribution of UTI Signs and symptoms No. with VUR	<u>Age distribution</u> 145/744 (19%) aged >1 year 35/744 (5%) aged 1-2 years 210/744 (28%) aged 2-4 years 249/744 (33%) aged 5-8 years 105/744 (14%) aged 9-12 years 246 (33%) with VUR 498 (67%) without VUR <u>Signs and Symptoms</u> Fever 312/744 (42%) Abdominal or loin pain 231/744 (31%) Enuresis 135/354 (38%) – only in children <5 years <u>VUR compared to no VUR</u> Fever 174/498 (35%) without VUR 140/246 (57%) with VUR (p=0.0004 NCC calculated) Abdominal pain 144/498 (29%) without VUR 86/246 (35%) with VUR	Definition of UTI not provided.

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
Dickinson JA; 1979 May 19 [36]	Study Type: Case-series Evidence Level: 3	To present clinical features of UTI and determine incidence in a rural area.	14 children with UTI (5 boys and 9 girls) Derived from a total population of 2879 (1446 boys and 1433 girls) Over an 18 month period	Children aged under 15 years attending a semi-rural GP practice. Infection diagnosed if bacterial counts in three consecutive samples exceeded 100000/ml by mid-stream or bag collection. 2 cultures completed in the GP surgery, and a confirmation culture at a laboratory.	Age distribution of UTI Signs and symptoms Frequency of clinical features of children presenting with UTI	156/2879 children presenting with symptoms of UTI, all were investigated (radiological investigations not reported) 14 of whom were found to have bacteriologically confirmed UTI. Incidence of urinary tract infection was 1.7 per 1000 boys at risk per year and 3.1 per 1000 girls. 2 boys and 4 girls presented with dysuria and frequency, 2 girls 1 boy with abdominal pain, one girls with haematuria and one boy with failure to thrive	Criteria to suspect UTI unclear. Symptoms only, or bacterial confirmation? Unclear whether the 156 sent for 'investigation' had urinalysis only, or had further investigations.

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
Hallett RJ;Pead L;Maskell R; 1976 Nov 20 [131]	Study Type: Case-series Evidence Level: 3	To present clinical and laboratory features of UTI in boys.	73 boys with suspected UTI 51 healthy controls.	Boys aged 2-12 years presenting to a GP clinic with suspected UTI (n=73) and healthy controls (n=51). Definite infection 10^8 organisms/L of a single organism Probable infection 10^7 organisms/L of a single organism Doubtful infection 10^7 organisms/L of mixed organisms. Matched for age and social class.	No. with UTI Presenting symptoms No. of recurrent infections.	49/73 definite infection 12/73 probable infection 12/73 doubtful infection Boys with definite or probable infection (n=61) 26/61 (43%) aged 2-5 years 35/61 (57%) aged 5-12 years <u>Signs and symptoms</u> Presenting symptoms in 49 boys with definite infection. Enuresis 22 (45%) Dysuria/frequency 40 (82%) Haematuria 10 (20%) Fever 13 (26%) Abdominal pain 17 (35%) Balanitis 10 (20%) Similar distribution of symptoms in boys with probable and doubtful infections.	Term 'recurrence' is not defined. No indication of time periods or organisms involved. Not all boys were followed up for the same length of time. Large range of follow-up times and no median/mean time reported.

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
Brooks D;Houston IB; 1977 Nov [129]	Study Type: Case-series Evidence Level: 3	To present the clinical findings of a study investigating children with UTI in general practice.	38 children (12 boys and 26 girls)	Children aged under 15 years presenting to a single GP practice with symptomatic UTI Bacteriuria defined as >10^5cfu/ml in a clean catch urine sample.	Frequency of clinical features of children presenting with UTI	Dysuria 27/38 (71%) Loin pain/tenderness 5/38 (13%) Vauge abdominal pain 12/38 (32%) Fever 8/38 (21%) Offensive urine 7/38 (18%) Enuresis 9/38 (24%) Daytime incontinence 2/38 (5%) Haematuria 1/38 (3%) Rigor 1/38 (3%)	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
Al Mugeiren M; 1996 [130]	Study Type: Case-series Evidence Level: 3	To describe the epidemiology, clinical features and therapeutic considerations of children with UTI in order to determine the most effective therapy.	1081 children 270 (25%) boys 811(75%) girls (boy to girl ratio 1:3)	Urine samples from inpatients, outpatients and emergency room patients with suspected urinary tract infections (fever, vomiting, dysuria, or urinary frequency) Positive urine culture $\leq 10^5$cfu/ml in a mid-stream sample.	Age distribution Presenting Symptoms Microoganism isolated	<u>Age distribution</u> 0-1 year 221 (20.4%) 1-2 years 265 (24.5%) 2-5 years 248 (22.9%) 5-12 years 347 (32.1%) <u>Signs and Symptoms</u> 0-1 year: fever and irritability 25/221 (11%) and vomiting 52/221 (23%) 1-2 years: fever and irritability 102/265 (38%) and vomiting 76/265 (29%) 2-5 years: fever and irritability 151/248 (60%), vomiting 37/248 (15%), frequency/dysuria 65/248 (26%), Enuresis 49/248 (20%), abdominal pain 61/248 (25%), lumbar pain 30/248 (12%) and foul-smelling or cloudy urine 31/248 (13%) 5-12 years: fever and irritability 167/347 (48%), vomiting 32/347 (9%), frequency/dysuria 134/347 (39%), Enuresis 95/347 (27%), abdominal pain 154/347 (44%) and lumbar pain 75/347 (22%).	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
Winberg J;Andersen HJ;Bergstrom T;Jacobsson B;Larson H;Lincoln K; 1974 [16]	Study Type: Case-series Evidence Level: 3	To describe the epidemiology, clinical features of children with UTI	521 children (419 girls and 90 boys)	Children aged 0-16 treated at a children's hospital or maternity unit for symptomatic UTI.	No. with UTI No. with fever	Almost all infants had fever, except neonates in whom only 42% had fever. After the first year of life, fever became less common. 1 – 12 months 179/186 (96%) 1-3 years 70/96 (73%) 3-10 years 120/200 (60%) 10-16 years 19/41 (46%) E.coli 83% of girls and 85% of boys under one year 60% of girls and 33% of boys aged 1 to 16 years. 57% of girls and 83% of boys in neonates(p=0.016) Proteus 33% of boys and 0% of girls over one year of age staphlycoccus albus 30% of girls and 12% of boys Recurrence Analysed in 419 girls 2 months to 1 year 53/124 (43%) 53 (43%) with fever, 0 without fever 1 to 3 years 33/87 (38%) 24 (28%) with fever, 9 (10%) without fever.	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
						3 to 11 years 78/187 (42%) 51 (27%) with fever, 27 (14%) without fever. 11 to 16 years 4/21 (19%) 3 (14%) with fever, 1 (5%) without fever. Overall 54% of the recurrences occurred within three months, 46% during the following 9 months.	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Follow up & Outcome measures	Effect size	Reviewer Comment
Hoberman A;Chao HP;Keller DM;Hickey R;Davis HW;Ellis D; 1993 Jul [14]	Study Type: x-sectional Evidence Level: 3	To determine the prevalence of UTI in febrile infants with and without source of fever	945 infants with febrile illness.	Febrile infants, aged 1 yr or less, seen in emergency who had urine culture results from Feb 1990 to Jan 1991 fever defined as rectal temp >=38.3C or axillary temp >=37.4C (in ER or in previous 24 hrs) UTI: all by bladder cath; >=10,000 cfu, single organism	Prevalence of UTI	50/945 (5.29%) febrile infants had UTI By fever source: 1/62 unequivocal 15/429 possible 34/454 no source p = 0.02 for possible v. no source	

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1 Urine collection

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Intervention & comparison	Effect size	Reviewer comment
Chu RWP;Wong Y;Luk S;Wong S; 2002 [138]	Study Type: RCT Evidence level: 1+	To determine the optimal method of SPA, the success rate of real time ultrasound-guided SPA compared with conventional SPA and factors associated with success.	30 infants randomly allocated to group A (for real-time ultrasound guided SPA) and 30 infants to group B (Blind SPA with prehydration protocol).	60 infants aged under 12 months were randomised to SPA. 30 infants in ultrasound guided group (19 boys, 11 girls) 30 infants in control group (8 boys and 22 girls) There were no significant differences in the age of infants (5.2 ± 3.4 months in ultrasound group vs. 4.2 ± 3.1 months in control group) p>0.05. In 36 infants (15 in group A and 21 in group B) SPA was performed because fever with positive urinalysis results. In 24 infants (15 in group A and 9 in	Infants in group A were not deliberately given any fluid before the first attempt For infants in group A undergoing ultrasound-guided aspiration, the bladder was scanned with an ultrasound scanner and bladder dimensions recorded. The bladder volume was calculated and aspiration wa performed if the bladder volume was estimated to be greater than 3ml. If the baldder volume was less than 3ml, a milk or juice feed was given and ultra-sound inspection repeated every 10-15 mins. Infants in group B were given 102 ± 47 ml of fluid before the first attempt at SPA which was performed after an interval of 25 ± 16 mins. For patients in group B undergoing conventional SPA, the infant had their	Overall success rates Ultrsound guided 26/30 (87%) 24/30 (80%) in the control group (p<0.05). First attempt Ultrasound success 18/30 (60%); failure 10/30 (33%); voided before attempt 2/30 (7%) Control success 18/30 (60%); failure 12/30 (40%) Equally successful in both groups (p>0.05) Second attempt Ultrasound: success 26/30 (60%); failure 2/30 (7%); voided before attempt 1/30 (3%) Control: success 6/30 (20%); failure 6/30 (20%) Third attempt Ultrasound: success 1/30 (3%); failure 0; no parental consent 1/30 (3%) Control: no parental consent 6/30 (20%) Urine collected by catheterisation Ultrasound: 4 (13%)	In control group Prehydration protocol used and bladder dullness demonstrated before SPA attempted. This may explain the differences between this study and others. In ultrasound guided group SPA was attempted regardless of the bladder volume.

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				group B) their previous bag urine sample was culture positive with mixed organisms or doubtful colony counts. No patient had clinical signs of dehydration.	nappy changed to ensure the recent voiding would be noticed and received a milk or juice feed. After 15 mins, the presence of the bladder was confirmed by light percussion and SPA was performed.	Control: 6 (20%) Ultrasound guided group Bladder depth in mm (mean ± SD) Successful attempts vs. unsuccessful attempts 28 ± 11 vs. 21 ± 5 (p<0.01) Calculated volume (ml) 17 ± 13 vs, 8 ± 6 (p<0.01) Bladder length 32 ± 12 vs. 23 ± 9 (p<0.05) Transverse width 33 ± 9 vs. 29 ± 5 (p>0.05) Control group No differences between successful attempts and failed attempts (time from last feed, amount of last feed, time from last void). Bladder dullness was demonstrated by light percussion 23/24 successful attempts vs. 8/18 failed attempts (OR 29.0, p<0.001)	
Kiernan SC;Pinckert TL;Keszler M; 1993 Nov [139]	Study Type: RCT Evidence level: 1+	To determine whether ultrasound guidance is useful to localise the position of	53 neonates	Neonates requiring SPA randomly assigned to an ultrasound-guided, or conventional urine aspiration between	Controls: No attempt at aspiration were made within 30 minutes of voiding. Ultrasound-guided:	Weight distribution and the level of operator training between the groups was similar. Success at first attempt Ultrasound 26/28 (93%)	

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		the bladder and to increase the amount of urine obtained.		July and December 1991. 28 in the ultrasound-guided group 25 controls	Neonates were scanned with a portable ultrasound scanner equipped with a 5MHz head. Both longitudinal and transverse views of the bladder were obtained. If the bladder measured at least 1x1cm SPA was attempted. Three passes at different angles (90,60 and 120 degrees) were attempted while the needle remained under the skin in both groups.	Control 7/25 (28%) p=0.001 Overall success (two attempts) Ultrasound 27/28 (96%) Control 15/25 (60%) p=0.003 Volume of urine obtained (ml) Ultrasound 2.1 ± 1.2 Control 1.3 ± 0.9 p=0.029 Number of passes Ultrasound 1.7 ± 1.0 Control 4.4 ± 2.0 p=0.001 Procedure time (seconds) Ultrasound 53 ± 59 Control 60 ± 40 p=0.600	
Gochman RF;Karasic RB;Heller MB; 1991 [140]	Study Type: RCT Evidence level: 1+	To determine whether portable ultrasound could improve the success rate of SPA in a paediatric ED.	66 children, 35 randomised to ultrasound (22 boys, 13 girls), 31 to no ultrasound (18 boys,	Children aged 0 to 15 months (median 1 month) old requiring urine collection by SPA between January and July 1989. 82% of children were less than 2 months old. No child was considered	All SPAs were performed by two clinicians. Neither investigator had any formal training in ultrasound technique. Ultrasound group Underwent scanning immediately following clinical evaluation. The ScanMate II	No significant differences between the groups in terms of age, weight or gender. 82% of children were less than 2 months old 2/66 full bladders identified by bladder percussion. Ultrasound Full bladder visualized in 16/35	Randomisation by random number tables Allocation concealment not described. Blinding not possible

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			13 girls)	significantly dehydrated. SPA was considered successful if any urine was aspirated Bladder was considered full if both anterioposterior and transverse maximum diameters were 2cm or more, and empty if either diameter was less than 2cm.	ultrasound scanner (a portable scanner) was used. If the bladder was full SPA was attempted, if empty, the bladder was rescanned 30 mins later. If the bladder remained empty SPA was not attempted and bladder catheterisation was performed. No ultrasound SPA perfoemed immediately after the clinical evaluation, provided the child had not voided in the past 30 mins, nor had a wet diaper at the time of evaluation. If the child had recently voided, SPA was delayed for 30 mins. Patients who either failed the SPA or wet a diaper during the waiting period underwent catheterisation.	(46%) after 30 minute waiting period an additional 3 patients met the criteria for full bladder 19/35 (54%). 15/19 (79%) of SPA attempts were successful. In 3/4 unsuccessful SPA attempts, catheterisation yielded ≥5ml of urine. 16/35 bladders remained empty on 2nd ultrasound scan and 15/16 had ≥5ml of urine was collected on catheterisation. No ultrasound 14/35 underwent SPA immediately and 17/35 had SPA performed after a 30 minute waiting period. 16/31 (52%) SPA attempts were successful In 11/15 unsuccessful SPA attempts, catheterisation yielded ≥5ml of urine. The success rate for the ultrasound group was significantly higher then for the controls (p=0.04) Operator efficiencies - increasing success rate over time (p=0.03) Ultrasound accurately detected the	

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						presence of urine in 19/21 children and the absence of urine in 25/29.	
Ozkan B;Kaya O;Akdag R;Unal O;Kaya D; 2000 [141]	Study Type: RCT published in a letter to the editor. Evidence level: 1+	To compare the success rates, number of passes and volume of urine obtained as well as complication rates of SPA with or without ultrasound guidance.	140 infants 70 ultrasound guided SPA (38 boys, 32 girls) 70 controls (42 boys, 28 girls	Infants under 2 years old and requiring SPA were randomised. The mean values of ages and weights were not different between groups. 35/70 (50%) in control group and 24/70 (34%) of the ultrasound guided group were under one month old. Exclusions: Patients with known intraabdominal pathology, history of bleeding disorders, or any degree of clinical dehydration.	Sterile 22 gauge needle attached to a 20ml syringe. Three passes at different angles (90, 120 and 60 degrees) while the needle remained under the skin. Control infants No SPAs were attempted within 30 minutes of voiding Ultrasound guided infants No SPAs were attempted unless the bladder measured 2x2cm. Scanned with ultrasound scanner and both longitudinal and transverse views of the bladder were obtained. All scans performed by the same rediologist. Aspirations under ultrasound guidance were performed under	Ultrasound guided vs. conventional, p-value SPA success 63/70 (90%) vs. 45/70 (64%), p<0.05 Volume obtained ~6ml for both groups (p>0.05) Passes Fewer passes in infants in the ultrasound guided group (p<0.05) In children under one month old, there were no differences in success rates between ultrasound guided (75%) and controls (74%) p>0.05. Complications Microscopic haematuria was observed in 5/140 (3.5%)	This study should be interpreted with some caution - it was published in a letter to the editor, therefore not all figures are available. Single operator - improvement with experience may account for higher success rates Unsure about number of attempts - "two attempts more than 30 minutes apart constituted

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					ultrasound during insertion of the needle		overall success or failure". Not enough information to understand whether the 'success' took more than one attempt.
Waddington P;Watson A; 1997 134	Study Type: Cohort Evidence level: 3	To evaluate the ease of application and reliability of different urine collection bags.	50 children (33 boys, 17 girls)	Children attending a children's clinic. No other details provided.	Intervention: The nurses first cleaned the genital area with warm tap water and cotton wool balls before applying the bag.	Hollister U-bags were used in 18 boys and 7 girls, while Urinicol bags were used in 15 boys and 10 girls. 8/25 Hollister u-bags leaked compared to 0/25 Urinicol bags ($p<0.01$)	
Al-Orifi F;McGillivray D;Tange S;Kramer MS; 2000 135	Study Type: Cohort Evidence level: 2+	To compare the risks of contaminated culture results and consequent adverse clinical outcomes in urine specimens obtained by urine collection bag compared to catheterisation.	7584 urine samples were collected from 4632 children.	Children ≤24 months who had a urine culture obtained by either urine collection bag or catheterisation between January 1993 and December 1995 at an emergency department or an outpatient unit. Negative: <103cfu/ml in a bag specimen, 102cfu/ml in a	Intervention: Bag urine cultures were obtained by Hollister U-bag after the perineum was cleansed with antibacterial soap and tap water. In the outpatient centre the bag was replaced after 30 minutes, while in the emergency department it was not. Catheter specimens were only collected in the emergency department after cleansing with iodinated soap and sterile water	7584 urine cultures 42.1% infants <6 months 25.9% infants between 6 and 11 months 31.9% from children between 12 and 24 months Bag specimens Emergency department: 2597 Outpatients: 2530 Catheter specimens Emergency department: 2457 Contamination Collection method: 54.4% bag vs.	

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				catheter specimen Positive: ≥104 cfu/ml in a bag specimen, ≥103cfu/ml in a catheter specimen Contaminated: two or more organisms cultured, or when a single organism was cultured in a concentration intermediate between a positive and negative.		9.0 catheter (p<0.001) Sex: 38.7% male vs. 29.2% female (p<0.001) Age: 31.4% <12 months vs. 38.7% 12-24 months (p<0.001) Leukocyte esterase: 32.3% positive vs. 33.7% negative (not significant) Odds Ratio (adjusted for age, sex and leukocyte esterase test) was 13.3 (95%CI 11.3 to 15.6) and when limited to the first urine culture in each child was OR 13.6 (95%CI 11.1 to 16.7)	
McKUNE I; 1989 [136]	Study Type: Cohort Evidence level: 3	To compare the contamination rates between bag and clean-catch urine collection methods.	46 urine samples (23 from each of two wards)	Children under 2 years old in one of two inpatient wards. No other details reported Exclusions: Children receiving antibiotic therapy and known to have gross renal abnormalities. Positive specimens: >105cfu/ml Inadequate specimens: When the specimen could not be interpreted No growth	Intervention: In Ward A, the child's genitalia was washed with soap and water and urine samples were collected in a sterile foil bowl. In ward B soap and water was used, followed by cleansing with sterile water and drying with cotton wool balls and urine collection bags, either Hollister U-bags or Simcare bags were applied.	46 urine samples (23 from each ward) were obtained; in ward A 44 attempts were made to obtain 23 urine samples, 18 of which were obtained in one hour or less. A parent was involved in 33 of the 44 attempts. Of the 11 times a nurse was involved, total time taken was 3 hours 25 minutes, however for 2 hours 15 minutes, nurses were also feeding the infants, therefore extra time taken overall was one hour 10 minutes. No specimens were contaminated In ward B 28 attempts were made to obtain 23 samples. The urine collection bags were in place for 15 minutes to 4 hours 10 minutes, with an average time of one hour 25	

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				Urine contaminated with faecal bacteria		minutes. 11 specimens were contaminated with faecal bacteria.	
Rao S;Bhatt J;Houghton C;Macfarlane P; 2004 Aug 133	Study Type: RCT Evidence level: 3	To evaluate a modified urine collection pad method for its ability to reduce heavy mixed growth bacterial contamination of urine collection pad samples in young children with suspected urinary tract infection.	68 children (37 single pads, 37 replaced pads)	Febrile children under 2 years old admitted to an acute medical ward with suspected UTI.	Children were randomised into two groups: a single urine collection pad that was left in the nappy until a sample had been obtained; or a urine collection pad that was replaced every 30 munited until a sample was obtained. Alarm sensors were placed in all urine collection pads. Urine was aspirated from the urine collection pads using a 20ml syringe and taken immediately to a lab for culture. UTI was defined as pure growth of a single organism >105cfu/ml.	80 children were recruited (42 in the single urine collection pad and 38 in the replaced urine collection pad), and urine collection failed in 12 children (5 single pad, 7 replaced pad) mainly because of faecal soiling of the pad and were excluded from the analysis. Baseline characteristics of the groups were similar with respect to age, however there were significantly more boys in the single pad group (25/37 vs. 13/31, p=0.034)) 3/68 (4%) children had a UTI. Single urine collection pad vs. replaced pad, p-value. UTI (>105cfu/ml) – 2/37 vs. 1/38 Mixed growth (>105cfu/ml) – 10/37 vs. 1/31 Mixed growth (<105cfu/ml) – 3/37 vs. 2/31 No growth – 22/37 vs. 27/31	

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McGillivray D;Mok E;Mulrooney E;Kramer MS; 2005 Oct[142]	Study Type: diagnostic Evidence Level: III	To compare the validity of the urinalysis on clean-voided bag versus catheter urine specimens using catheter culture as the gold standard	303 children (102 boys, 201 girls)	Non-toilet-trained children under 3 years old who presented to a children's emergency hospital between June 2000 and December 2001. Inclusion: Fever without source (>39C) or any fever >48 hours duration and males under 6 months or females under 12 months, uncircumcised boys of any age, past history of UTI or abnormal renal anatomy. Another group of children without fever were also included if they were Ill-appearing without identifiable focus of infection or infants under 3 months exhibiting signs or symptoms of UTI (dysuria, foul-smelling urine,	Bag urine (collected first) A positive dipstick was defined as the presence of greater than a trace (Ca15/mm^3) leukocyte esterase or a positive nitrite result. The catheter urine culture was considered positive if it yielded >10^3cfu/ml or >10^6cfu/ml of a single pathogenic organism.	Only children with bag and catheter urine specimens were evaluated. 54/303 (18%) were under 90 days old. 82 of the catheter cultures were positive. Dipstick in paired bag vs catheter specimens (2 age groups) Sensitivity Overall: Bag 85% (78% to 93%) vs. catheter 71% (61% to 81%) p=0.003 ≤90 days: Bag 69% (44% to 94%) vs. catheter 46% (19% to 73%) p=0.248 >90 days: Bag 88% (81% to 96%) vs. catheter 75% (65% to 86%) p=0.016 Specificity Overall: Bag 62% (56% to 69%) vs. catheter 97% (95% to 99%) p<0.001 ≤90 days: Bag 61% (46% to 76%) vs. catheter 100% (93% to 100%) p<0.001 >90 days: Bag 63% (56% to 70%) vs. catheter 97% (94% to 99%) p<0.001 Dipstick and microscopy in paired bag vs catheter specimens (2 age groups)	No way of knowing how many children did not have a catheter sample (ie. Only had a bag sample and therefore were not analysed)

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				change in urine colour) or had unexplained abdominal pain. Exclusions: children requiring urgent medical attention, children already receiving antibiotics		Sensitivity Overall: Bag 95% (90% to 100%) vs. catheter 83% (74% to 91%) p=0.004 ≤90 days: Bag 77% (54% to 100%) vs. catheter 62% (35% to 88%) p=0.480 >90 days: Bag 99% (96% to 100%) vs. catheter 87% (78% to 95%) p=0.013 Specificity Overall: Bag 45% (38% to 52%) vs. catheter 95% (92% to 98%) p<0.001 ≤90 days: Bag 54% (38% to 69%) vs. catheter 100% (92% to 100%) p<0.001 >90 days: Bag 43% (35% to 50%) vs. catheter 94% (90% to 98%) p<0.001 Dipstick in paired bag vs catheter specimens (boys and girls, 2 age groups) Sensitivity Boys overall: Bag 86% (74% to 99%) vs. catheter 69% (52% to 86%) p=0.131 Boys ≤90 days: Bag 73% (46% to 99%) vs. catheter 45% (16% to 75%) p=0.248 Boys >90 days: Bag 94% (84% to 100%) vs. catheter 83% (66% to	

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						100%) p=0.617 Girls overall: Bag 85% (75% to 95%) vs. catheter 72% (60% to 84%) p=0.023 Girls ≤90 days: Bag 50% (0% to 100%) vs. catheter 50% (0% to 100%) p=1 Girls >90 days: Bag 86% (77% to 96%) vs. catheter 73% (60% to 85%) p=0.023 Specificity Boys overall: Bag 86% (78% to 94%) vs. catheter 99% (96% to 100%) p=0.027 Boys ≤90 days: Bag 100% (79% to 100%) vs. catheter 100% (79% to 100%) p=1 Boys >90 days: Bag 83% (73% to 93%) vs. catheter 98% (95% to 100%) p=0.027 Girls overall: Bag 51% (43% to 59%) vs. catheter 97% (94% to 100%) p<0.001 Girls ≤90 days: Bag 41% (22% to 59%) vs. catheter 100% (89% to 100%) p<0.001 Girls >90 days: Bag 53% (44% to 62%) vs. catheter 96% (92% to 99%) p<0.001 Dipstick in paired bag vs catheter specimens in toilet trained children (n=249) aged >90 days using different colony counts	

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						Sensitivity 103cfu/ml: Bag 88% (81% to 96%) vs. catheter 75% (65% to 86%) p=0.016 104cfu/ml: Bag 93% (87% to 100%) vs. catheter 81% (73% to 90%) p=0.046 105cfu/ml: Bag 96% (90% to 100%) vs. catheter 83% (74% to 91%) p=0.077 Specificity 103cfu/ml: Bag 63% (56% to 70%) vs. catheter 97% (94% to 99%) p<0.001 104cfu/ml: Bag 61% (54% to 68%) vs. catheter 94% (91% to 97%) p<0.001 105cfu/ml: Bag 59% (52% to 65%) vs. catheter 90% (86% to 94%) p<0.001	
Schroeder AR;Newman TB;Wasserman RC;Finch SA;Pantell RH; 2005 Oct [143]	Study Type: diagnostic Evidence Level: II	To determine predictors of urethral catheterisation in febrile infants and to compare bag and catheterised urine test	From a larger study (Febrile Infant Study) involving 219 practices,	Children aged under 93 days with temperature of 38°C or higher who underwent urinalysis and urine culture. For SPA, at lease 100 cfu/ml, for catheter 20000	Urine collection bags compared to catheterisation.	Bag LE sensitivity: 76% LE Specificity: 84% N sensitivity: 25% N specificity: 98% Catheter LE sensitivity: 86% LE Specificity: 94%	

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		performance characteristics.	3066 infants were enrolled, 1482 had both urinalysis and culture, 1384 who had urine collected by catheter or bag and were evaluated.	cfu/ml, for bag and clean catch at least 100000 cfu/ml		N sensitivity: 43% N specificity: 99% Further analysis of 54 patients who had false positive results for LE on bag urinalysis. Of the children who were also tested for nitrites, 4/1 (8%) had positive results. Of children who were also tested for urine white blood cell counts 9/47 (19%) had more than 10 WBC/hpf. If children who had urine samples with positive LE and positive nitrite reasuls, more than 10 WBC/hpf, or ambiguous culture results are considered to be positive for UTI, the difference between the methods in specificity for LE is still significant. (bag 89%, catheter 95%, p<0.001) Likelihood ratios for urine WBC counts, by urine collection method. Bag 0-2 WBC/hpf – 0.6 3-5 WBC/hpf – 1.1 6-10 WBC/hpf - 0 11-20 WBC/hpf - 7 >20 WBC/hpf – 13.5 ROC curve (95%CI) – 0.71 (0.61 to 0.82)	

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						Catheter 0-2 WBC/hpf – 0.2 3-5 WBC/hpf – 1 6-10 WBC/hpf – 3.7 11-20 WBC/hpf – 23.9 >20 WBC/hpf – 26.3 ROC curve (95%CI) – 0.86 (0.82 to 0.91) The area under the ROC curve for urine WBC counts and UTI was higher in children with catheter samples than in those with bag samples (0.86 vs. 0.71, p=0.01).	
Liaw LCT;Nayar DM;Pedler SJ;Coulthard MG; 2000 [144]	Study Type: Case-series Evidence Level: 3	To assess contamination rates and parents preferences for collecting urine at home.	44 parents collecting urine from 29 boys and 15 girls	Infants aged 1 to 18 months	Pads were placed inside the nappy and checked every 10 minutes until wet, then urine aspirated with a syringe. Bags were applied and inspected every 10 mintues and removed to decant urine. Clean catch samples were collected in a sterile bottle. Samples were immediately instilled on dipslides with sterile swab sticks.	Parents preferred using the pad first, the bag second and the clean catch method third. Seven samples from pads, eight from bags and one from clean catch had contamination. Nine samples from 5 children grew >10^5 coliforms/ml suggesting infection, however these were excluded by sterile samples collected on the same day in hospital. Parents found pads and bags easy to use and preferred them to the clean catch method. The pad was considered comfortable, whereas the bag was distressing, particularly on removal often	No information about why children needed urine collected. Volunteer sampling method so not representative of the population. All urine was collected on the same day, so likely bias to the the methods not used first.

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						leaking and leaving red marks. Some found extracting the urine from the pad or emptying the bag awkward. Most parents complained that the clean catch method was time consuming and often messy and nine parents gave up after prolonged attempts.	
Kozer E;Rosenbloom E;Goldman D;Lavy G;Rosenfeld N;Goldman M; 2006 Jul [137]	Study Type: RCT Evidence Level: 2+	To compare the severity of pain during SPA with pain during trans-uretrhral catheterisation in infants younger than 2 months.	51 infants (31 boys, 20 girls)	Infants 0-2 months of age presenting to an emergency department with fever (rectal temperature >38C) and requiring a urina culture between April 2004 and April 2005. Exclusions: Premature birth, previous sepsis workup or other painful procedures, anomaly of the urogenital system or abdominal wall or had a known allergy to local anaethetic.	Pain outcomes were measured on three scales: 1. The nurse and one of the child's parents were asked to rank the infants pain on a 100-mm visual analog scale (VAS where 0 means no pain and 10 means worst possible pain) 2. The upper part of the infants body was video-taped during the procedure and one investigator assigned a point score according to the Douleur Aigue di Nouveaune (DAN) neonatal actue pain scale from 0 no pain, to 10 maximal pain based on three parameters; facial expression, limb movement, and vocal expression. 3. The same investigator measured the duration of	Baseline characteristics Male/female – 17/10 vs. 14/10, p=0.78 Age (±sd) in days – 27.7 (±14.8) vs. 36.5 (±12.3), p=0.007 Weight (±sd) in kgs - 4.03 (±1.2) vs. 4.37 (±0.8), p=0.25 Pain Assessment SPA vs. catheter, difference between SPA and catheter (95%CI of the difference) DAN, mean (±sd) - 7.0 (±1.9) vs. 4.5 (±2.1), 2.5 (1.4 to 3.7) VAS by a parent, mean (±sd) mm – 63 (±27) vs. 46 (±26), 16.8 (1.8 to 31.8) VAS by nurses, mean (±sd) mm - 63 (±18) vs. 43 (±25), 19.6 (7.4 to 31.8) Duration of cry, mean (±sd) s – 62.9 (±26) vs. 49.7 (±35.7), 13.2 (4.3 to 30.7)	

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					the cry from the beginning of the procedure until the cry had stopped for at least 5 seconds.		

1 Urine preservation

Bibliographic Information	Study Type & Evidence Level	Study aims	Number of Patients & Characteristics	Intervention	Results	Reviewer Comment
Eriksson I;Lindman R;Thore M; 2002 [145]	Study Type: Comparative Laboratory study Evidence Level: 3	To evaluate a commercial tube prepared with boric acid, sodium formate and sorbitol..	154 patients from eight health centres. Urine samples were collected from consecutive outpatients with suspected acute urinary tract infection. Patients on antibiotics and children below 10 years of age were excluded.	Conventional tubes (styrene tubes 11ml, Cerbo, Sweden) and tubes with bacteriostatic properties (Hemogard Vacutainer (HG) and Becton-Dickinson). Urine was divided into three tubes. One conventional tube was sent to the laboratory by ordinary chilled transport. Another conventional tube and one HG tube were transported to the laboratory without chilling. Cultures were performed upon arrival at the laboratory and then 24, 48 and 72 hours after primary sampling.	Of the 154 patients studied, 144 had positive cultures (>10^6cfu/L) 24 hours after sampling there were no significant differences in bacterial counts between the chilled conventional tubes and the HG tubes at room temperature. However, in the HG tubes a significant change in *enterococcal* counts were noted after 48 hours.	

Bibliographic Information	Study Type & Evidence Level	Study aims	Number of Patients & Characteristics	Intervention	Results	Reviewer Comment
Lauer BA;Reller LB;Mirrett S;Ferris JA; 1983 Jan [146]	Study Type: Observational Evidence Level: 3	To learn whether or not chemical preservatives in the Becton-Dickinson urine culture kit are useful for the transport of urine for routine urinalysis.	304 women Clean-catch urine specimens were collected from pregnant women visiting an obstetric clinic.	Urine samples were collected in a sterile plastic cup and distributed into a Becton-Dickinson urine culture kit and a sterile glass tube with out preservative.	Of the 304 urine specimens obtained from pregnant women 2% had significant bacteriuria (10^5cfu/ml). There was complete agreement between preserved and unpreserved split samples in the detection of glucose, ketones, bilirubin and blood. Of the 388 women with symptoms of UTI seen in the emergency room or outpatients department 198 (51%) had significant bacteriuria. Urine microscopy revealed a tendency for erythrocyte counts to be diminished after 24 hours at room temperature in unpreserved specimens. Gram stain results of preserved and unpreserved split samples were comparable; staining characteristics were not altered by the preservative.	

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Watson PG;Duerden BI; 1977 Jun [147]	Study Type: Observational Evidence Level: 3	To compare methods of preservation with simulated specimens of pooled urine seeded with known concentrations of test organism.	Number of patients/samples unknown Midstream urine was collected from healthy adult males who had not taken antibiotics in the last three days. Urine was collected on a single day and pooled and sterilized.	One strain each of *E.coli, Pseudomonas aeruginosa, Klebsiella aerogenes, Proteus mirabilis, Micrococcus* and *Streptococcus faecalis* were isolated from infected urine. An overnight culture of each test strain in pooled urine was serially diluted to give six simulated specimens of 10, 103, 104, 105, 106 and 107. 1. At room temperature (night time min 14°C, day time max 27°C) 2. In a domestic refrigerator (min 2°C, max 9°C) 3. 0.16g of powdered boric acid dissolved in 9ml of urine to give a 1.8% solution held at room temperature (min 10°C max 28°C). 4. 30% NaCl – 3 PVP solution held at room temperature (min 18°C, max 28°C). 5. A NaCl – PVP solution held at room temperature (min 18°C, max 27°C)	Unpreserved specimens at room temperature Each test strain multiplied rapidly and the surface viable counts showed concentrations of between 107 and 10^8cfu/ml within 72 hours in every specimen. Refrigerated specimens The surface viable counts for all the specimens remained constant for 72 hours. Specimens with 1.8% boric acid The surface viable counts remained constant for 24 hours, but he viable counts of specimens infected with *P.aeruginosa* fell markedly. After 24 hours the viable counts of the *E.coli* specimens, except for the most heavily infected specimen declined. The viable counts of specimens in the *Klebsiella aerogenes*, *Proteus mirabilis*, *Micrococcus* and *Streptococcus faecalis* and the specimen that was most heavily infected with *E.coli* remained constant for 72 hours. Specimens with 9% NaCl – 0.9% PVP There were no differences between the results obtained with PVP of the two molecular weights. The surface viable counts of all specimens of *E.coli* fell	Urine only collected from adult males Only used viable counts – rather than culture

Bibliographic Information	Study Type & Evidence Level	Study aims	Number of Patients & Characteristics	Intervention	Results	Reviewer Comment
					markedly within 24 hours, except the viable count of the most heavily infected specimen which fell more slowly. The viable counts of the most heavily infected *K.aerogenes* remained constant while the other specimens fell more slowly. The strain of *Micrococcus* grew in the specimens however after 24 hours the viable counts remained in the same range that they were in at time zero. The viable counts of *Streptococcus faecalis* specimens remained constant for 72 hours, but the viable counts of all specimens in the Proteus mirabilis and *P.aeruginosa* specimens fell markedly within 24 hours.	

Bibliographic Information	Study Type & Evidence Level	Study aims	Number of Patients & Characteristics	Intervention	Results	Reviewer Comment
Southern PM;Luttrell B; 1984 Jun [148]	Study Type: Observational Evidence Level: 3	To evaluate the efficacy of collecting urine specimens in Becton-Dickinson tubes and subsequently screening them for bacteriuria with the Abbott MS-2.	312 adults Midstream urine specimens were collected from obstetric outpatients attending a clinic for prenatal care. Some patients had suspected UTI and others were asymptomatic. Urine was collected by mid-stream catch and placed in the Becton-Dickenson tube and another in a screw-cap tube routinely used for transporting urine from the hospital to the laboratory. If samples could not be transported within 20 minutes, the conventional	The Abbott MS-2 is an automated system that allows screening of urine specimens for significant bacteriuria.	Of the 312 urine specimens included in the study, 124 were positive for bacteriuria. The median time required for urine specimens to be judged positive by the MS-2 was similar for conventional tube and for Becton-Dickenson tubes (95 and 105 minutes respectively). Bacterial specimen results from conventional tubes did not differ significantly from those from Becton-Dickinson tubes. Culture results from 24 hour delayed samples from the Becton-Dickinson tubes were significantly different in that 40 of the 188 specimens had colony counts in excess of 10^5cfu/ml.	In obstetric population – could be quite different to urine in children.

Bibliographic Information	Study Type & Evidence Level	Study aims	Number of Patients & Characteristics	Intervention	Results	Reviewer Comment
			tube was refrigerated. The time necessary for the MS-2 to judge a urine sample positive was recorded for both specimens.			
Raff LJ;Bazzetta K; 1985 [149]	Study Type: Observational Evidence Level: 3	: To determine whether boric acid interferes with the reactions of the Chemstrip LN dipstick.	177 adult patients. Patients included inpatients, outpatients and residents of a nursing centre.	Preliminary study: Specimens negative for leukocyte esterase and nitrite were obtained by multiple mid-stream urine collections into disposable non-sterile urine cups from one asymptomatic volunteer	Preliminary studies with the LN+ and LN- samples preserved in boric acid demonstrated no evidence of interference with the LN strips immediately after preparation, or after the 2 hour incubation. The dipstick correctly indicated the presence or absence of nitrite and	Unknown whether these results can be applied to dipsticks in general.

Bibliographic Information	Study Type & Evidence Level	Study aims	Number of Patients & Characteristics	Intervention	Results	Reviewer Comment
				male. Specimens positive for leukocyte esterase and nitrite were prepared by placing Chek-Stix urinalysis control strips in 12ml deionized water, following the manufacturers instructions. The positive and negative samples were then transferred to numbered Sage collection tubes containing boric acid. 21 samples (12 negative and 9 positive) were tested immediately following preparation and tested again after 2 hours. Technicians were blind to the composition of each specimen. Main study: 177 consecutive clinical urine specimens preserved in boric acid were evaluated before routine culturing.	leukocyte esterase in all cases.	

Bibliographic Information	Study Type & Evidence Level	Study aims	Number of Patients & Characteristics	Intervention	Results	Reviewer Comment
Lauer BA;Reller LB;Mirrett S; 1979 Jul [150]	Study Type: Observational Evidence Level: 3	To evaluate the boric acid-glycerol-sodium formate preservative in the Becton-Dickinson urine culture kit and to evaluate the use of ordinary paper cups for collection of urine.	1000 urine samples sent to a hospital microbiology laboratory. Children and adults with symptoms suggesting UTI and from pregnant women being screened for asymptomatic bacteriuria.	Upon arrival in the laboratory, specimens were refrigerated immediately. Each specimen was cultured 4 times. 1. An initial reference culture 2. A portion of urine was poured into a clean nonsterile paper cup, aspirated into a urine transport tube and recultured immediately. 3. Original specimen paper cup was refrigerated for 18 to 24 hours. 4. Urine transport tube held at room temperature for 18 to 24 hours.	88 of the initial reference cultures were positive (pure growth of 10^5cfu/ml). 82 (93.2%) of the 88 specimens on reference culture were also positive after refrigeration or holding at room temperature in the transport tube for 24 hours. There was one false positive culture from refrigerated urine but none from the transport tube. Mixing urine in the non-sterile container did not introduce detectable contamination.	

Bibliographic Information	Study Type & Evidence Level	Study aims	Number of Patients & Characteristics	Intervention	Results	Reviewer Comment
De la Cruz E;Cuadra C;Mora JA; 1971 Jul [151]	Study Type: Observational Evidence Level: 3	To study the effect of time, temperature and glucose content on the growth of two initial populations of either *E.coli* or *P.vulgaris* in sterile urine samples.	No information about patients or samples.	All men entering the bathroom of a laboratory were requested to void urine into a two litre flask. The urine collected was sterilized by Seitz filtration not more than three hours after thee flask was left in the bathroom and divided into portions. One of the samples was used for determination of glucose, albumin and pH. The remaining urine was stored at 10°C. To strains of *E.coli* and two of *P.vulgaris* were isolated from patients with urinary tract infections.	Urine containing no glucose: The original number of bacteria both in the urines and the controls showed little or no change over time. Populations of *P.vulgaris* remained unchanged at all three temperatures while *E.coli* showed a slight increase over time. Urine containing glucose: All bacterial strains studied showed reductions in the populations after two hours of incubation at -10°C and continued to decline at 4 hours and 8 hours. However, there was a steady increase in bacterial numbers with time in the samples incubated at room temperature (25°C) which showed at least 10^5 organisms within 4 hours. The bacterial populations showed almost no change when the incubation temperature was 4°C regardless of bacterial strain.	No other studies investigate glucose so not enough information to draw any firm conclusions. No information about the urine samples or the patients they were collected from. Very old study (1971) so laboratory SOPs may have changed (?)

Bibliographic Information	Study Type & Evidence Level	Study aims	Number of Patients & Characteristics	Intervention	Results	Reviewer Comment
Nickander KK;Shanholtzer CJ;Peterson LR; 1982 Apr [152]	Study Type: Observational Evidence Level: 3	To determine the minimum amount of urine necessary to obtain accurate results with each system.	240 specimens Patients characteristics not reported	The Sage urine culture tube and the Becton-Dickinson culture tube were evaluated by using 30 cultures diluted in urine to 10^5cfu/ml. Both tubes were injected with 1, 2, 3 and 4-5 ml (tube capacity) of urine containing each culture. Specimens were held at 22°C and cultured at 0, 4 and 24 hours.	The Becton-Dickinson urine culture kits were toxic to *E.coli* and *Klebsiella pneumoniae* in specimens containing up to 2ml of urine. The minimum useable amount of urine for reliable results was 3ml. The Sage urine culture tube maintained the number of bacteria in 1 to 4.5ml of urine in 83% of the specimens. However the Sage tube was toxic to *E.coli* when held for 24 hours. Quantitative counts of *enterococci* tended to significantly increase in specimens that contained 2ml or more of urine in either system.	

Bibliographic Information	Study Type & Evidence Level	Study aims	Number of Patients & Characteristics	Intervention	Results	Reviewer Comment
Wheldon DB;Slack M; 1977 Jul [153]	Study Type: Observational Evidence Level: 3	To quantitatively investigate the multiplication of contaminant bacteria in urine and attempt to define the duration of delay during which bacterial culture can be expected to give a reliable indication of the presence or absence of urinary infection.	106 patients. Patients attending a health centre and from members of the hospital staff. Individuals with known diabetes, urinary tract abnormalities and those receiving antimicrobial therapy were excluded.	Cultures were performed within one hour of voiding and successive cultures were carried out at 2, 4, 8, 12 and 24 hours after voiding. Throughout the period of sampling, specimens were kept between 19°C and 23°C	Freshly voided urine 14 of the 41 urine samples from males (34%) and 5 of 65 from females (7.7%) had bacterial populations of less than 10^2cfu/ml. None of the urines from males had bacterial counts in excess of 10^5cfu/ml, while four urines from females (6.2%) had counts exceeding 10^5cfu/ml. Multiplication of bacteria Enterococci, E.coli, S albus an group B streptococci were the organisms which most commonly multiplied in urine to give counts in excess of 10^5cfu/ml within 24 hours of voiding. The lag phase was usually short and frequently undetectable. *Enterobacteria* other than *E.coli* were rarely isolated more than 10^2cfu/ml when sampling was carried out but at later samplings showed growth patterns silimar to *E.coli*. All isolates grew exponentially after approximately 8 hours, and most had a lag time of approximately 4 hours.	

Bibliographic Information	Study Type & Evidence Level	Study aims	Number of Patients & Characteristics	Intervention	Results	Reviewer Comment
Jefferson H;Dalton HP;Escobar MR;Allison MJ; 1975 Nov [154]	Study Type: Observational Evidence Level: 3	To determine the effect of transport delay on the microflora of clinical specimens collected for microbiological analysis.	Number of patients/samples not reported. On a medical ward of a hospital. No other information reported	Clean catch urine specimens were collected from patients on medical wards. Proportions of these specimens were cultures approximately 10 minutes after collection for aerobic organisms. The remainder of each specimen was kept at room temperature until collected by the transportation service.	The time necessary for transportation of the urine specimens ranged from 2 to 5 hours with an average of 4 hours. The results from 100 urine specimens cultured immediately after collection indicated that 71% had colony counts of less than 102; 14% between 104 and 105; and 15% more than 106. After transportation 71% maintained colony counts of less than 102; 9% between 104 and 105; and 20% more than106.	Not enough information to draw any clear conclusions about urine collection. No original N, no information about blinding, no information about patients

Bibliographic Information	Study Type & Evidence Level	Study aims	Number of Patients & Characteristics	Intervention	Results	Reviewer Comment
Lewis JF;Alexander JJ; 1980 [155]	Study Type: Observational Evidence Level: 3	To provide evidence about the validity of overnight refrigeration for quantitative bacteriological evaluation.	Of 414 urine cultures, there were 109 cultures with colony counts of 104 cfu/ml or higher.	Initial urine cultures (less than 2 hours old), compared with refrigerated urine cultures.	Four cultures change from sterile to significant colony count 105 cfu/ml or greater, all of which were S aureus. A single culture changed from 105 cfu/ml to sterile where the organism involved was E.coli. Nine other cultures exhibited some change in colony count of which a number of organisms were involved in the discrepancies.	

Bibliographic Information	Study Type & Evidence Level	Study aims	Number of Patients & Characteristics	Intervention	Results	Reviewer Comment
RYAN WL;MILLS RD; 1963 May [156]	Study Type: Observational Evidence Level: 3	To determine if bacterial concentrations generally considered insignificant (less than 10,000/ml) many become significant as a result of bacterial multiplication in the urine during refrigeration.	Unknown number of patients/samples Urine obtained from 'normal' males and females – no other information reported.	Following collection (clean catch) the specimens were refrigerated at 5°C for approximately 24 hours. The urine was then pooled, sterilized by pressure filtration and stored at 5°C in 100ml aliquots in sterile bottles. Two bottles were inoculated for each of the bacteria employed and the bottles were placed at 0.5°C, 5°C, 10°C and 15°C. Every 24 hours for 4 days samples of urine from each bottle were cultured.	At 0.5°C, 5°C and 10°C, *E.coli* remained largely unchanged. At 15°C, *E.coli* grew from 12,000/ml immediately after collection to 16,000/ml at 24 hours, 370,000/ml at 48 hours and reached 800,000/ml by 72 hours. Bacterial counts overall remained the most stable in the 5°C group.	

1 Urine testing

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Deville WL;Yzerman s JC;van Duijn NP;Bezemer PD;van der Windt DA;Bouter LM; 2004 Jun 2 [157]	Meta-analysis Evidence level: II	To summarise the available evidence on the diagnostic accuracy of the urine dipstick test, taking into account various pre-defined potential sources of heterogeneity	220 articles of which 72 met inclusion criteria - 17 studied nitrites only, 2 studies leukocyte esterase only and the remaining studies evaluated combinations of both.	Presented results by patient group (pregnant women, elderly, urology, children etc)	Dipstick tests for nitrites and/or leukocytes compared to culture	Accuracy of nitrites was higher in pregnant women (Diagnostic odds ratio = 165) and in elderly people (DOR = 108). Positive predictive values were ≥80% in elderly and in family medicine. Subgroup analysis of diagnostic accuracy found ten studies of nitrite dipstick tests in children. Sensitivity 0.50 (0.42, 0.60), specificity 0.92 (0.87, 0.98) with a DOR 34 (12, 97). Accuracy of leukocyte esterase was high in studies in urology patients (DOR = 267). Sensitivities were highest in family medicine (86%). Negative predictive values were high in both tests in all patient groups and settings except in family medicine. The combination of both test results showed an increase in sensitivity. Accuracy was high in studies in urology patients (DOR = 52), in children (DOR = 46) and if clinical information was present (DOR = 28). Sensitivity was highest in studies carried out in family medicine (90%). Predictive values of combinations of positive	No information about quality assessment including blinding

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
						test results were low in other situations. Subgroup analysis of accuracy of nitrite and leukocyte esterase dipsticks in combination found nine studies of nitrite dipstick tests in children. Sensitivity 0.83 (0.78, 0.89), specificity 0.85 (0.79, 0.91) with a DOR 46 (23, 95). Using a pre-test probability (prevalence) of 0.20, based on the pooled sensitivities and specificities of the studies, for nitrites, the PPV in children was 61% and the NPV 88%; for leukocyte esterase the PPV in children was 34% and the NPV 88%; for one or both dipsticks positive, the PPV in children was 58% and the NPV 95%; for both dipsticks positive, the PPV in children was 66% and the NPV 87%.	

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Doley A;Nelligan M; 2003 Feb [158]	Retrospective case note review Evidence Level: II	To determine if dipstick urinalysis in the paediatric population is an adequate screening tool to exclude UTI..	Records of 6618 paediatric presentations over an 8 month period. 375 patients analysed	Retrospective case-note review of children presenting to a paediatric department. Urine collection was either by bag or clean-catch except in four cases of SPA. Specifically looking at two age groups: 0-2 years and 2-10 years. Positive urine culture was defined as greater than 10^5cfu/ml of an isolated organism.	Bayer Clinitek 50 urinalysis machine using Bayer multistix 10 SG reagent strips compared to culture	The sensitivity of the dipstick in all cases was 92.5% (95%CI 84.3 - 100%), specificity 39.4% (95%CI 34.2 - 44.6%), positive predictive value 15.4% (95%CI 10.8 - 20%) and negative predictive value 97.8% (95%CI 95.3 - 100%). The sensitivity of the dipstick in children aged 0-2 years was 87.5% (95%CI 74.3 - 100%), specificity 39.7% (95%CI 31.5 – 47.9%), positive predictive value 20.4% (95%CI 12.6 – 28.2%) and negative predictive value 94.7% (95%CI 88.9 - 100%). The sensitivity of the dipstick in children aged 2-10 years was 100% (95%CI 100 - 100%), specificity 39.2% (95%CI 32.4 – 46%), positive predictive value 11.0% (95%CI 5.8 – 16.3%) and negative predictive value 100% (95%CI 100 - 100%).	Used in a sample of patients relevant to our population and used valid reference standard. Use of medical records and other retrospective data introduces potential bias. Specificity data low compared with other studies. No information about blinding.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Pugia MJ;Sommer RG;Kuo HH;Corey PF;Gopual DL;Lott JA; 2004 Mar [159]	Study Type: Diagnostic Evidence Level: II	To assess the clinical utility of new, pathogen-specific tests to be applied with widely used dipsticks..	1743 patients. 1132 females, 611 males.	Patients with suspected UTI. No information about age of patients.		Combination of leukocyte and nitrite dipsticks gave negative predictive values of 93% for culture-negative samples. Using the same dipsticks on culture positive samples, the positive predictive values were unacceptably low. The false negative rate for leukocyte esterase or nitrite dipstick tests was 5% (80/1743), false positive rate 17% (304), True positive rate 15%(262) and true negative rate 63% (1097). The positive predictive value was 46% and the negative predictive value 93%. The false negative rate for the Immuno-chromatography strip was 10% (168/1743), false positive rate 2% (42), True positive rate 10% (174) and true negative rate 78% (1359). The positive predictive value was 81% and the negative predictive value 89%. The false negative rate for combination leukocyte esterase, nitrite dipstick and immuno-chromatography tests was 11% (190/1743), false positive rate 1% (19), True positive rate 9% (152) and true negative rate 79% (1382). The positive predictive value was	No information about blinding May not be in a suitable group of patients.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
						89% and the negative predictive value 88%.	

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Hiraoka M;Hida Y;Mori Y;Tsukahara H;Ohshima Y;Yoshida H;Mayumi M; 2005 [160]	Laboratory study method.. Evidence Level: II	Compared the accuracy in diagnosing significant bacteriruia between quantitative unspun-urine microscopy and the gram-stain	325 urine samples obtained at random from 130 patients	67 males and 63 females aged 3 months to 94 years (mean 37.7 years). 301 mid-stream samples and 24 catheterised samples. 43 samples collected at outpatients and 282 from inpatients. 109 samples from patients being treated with antibiotics 216 from patients without antibiotic treatment.	Gram stain and quantitative unspun urine microscopy compared to culture.	Significant bacteriuria was detected by urine culture in 37 out of 325 urine samples. Unspun-urine microscopy samples in cell-counting chambers were negative in 248 samples, positive in 33 and ambiguous in 44. Ambiguous samples were subjected to oil-immersion microscopy which made it possible to identify rods, cocci, salts or other particles. Overall, unspun-urine microscopy was able to detect bacteriuria in 35 of 37 urine samples with culture-proven significant bacteriuria (sensitivity 94.6%), failing to identify bacilli in two urine samples. Unspun-urine microscopy identified 286 of 288 urine samples with negative culture results (specificity 99.3%) Gram-stain method was able to detect bacteriuria in 33 of 37 urine samples with culture-proven significant bacteriuria (sensitivity 89.2%). Gram-stain method identified 284 of 288 urine samples with negative culture results (specificity 98.6%) Both methods, the unspun	No blind comparison Two thirds of the patients were being treated with antibiotics.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
						microscopy and the Gram stain were similarly reliable when compared with culture.	

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Ciancaglini E;Fazii P;Sforza GR; 2004 [161]	Evidence Level: III	Compared the accuracy of the differential fluorescent staining method and the Gram stain method in screening for bacteriuria compared to conventional culture	1487 urine samples were tested	Hospitalised patients and outpatients. Urine collected using a sterile technique.	Study describes a differential fluorescent staining method which distinguishes Gram positive from Gram negative bacteria in fluorescence compared with conventional culture (greater than or equal to 10^4cfu/ml)	A total of 1487 urine samples were tested. 289 were found to have colony counts greater than 104 cfu/ml; 237 yielded a single organism and 52 a mix of two or more organisms. Of the 237 yielding a single organism 224 were detected by the differential fluorescent staining method and 162 by the Gram stain (13 undetected by the differential fluorescent staining method and 75 undetected by the Gram stain). The sensitivity of the differential fluorescent staining method was 94.5% while the sensitivity of the Gram stain was 68.3%. The specificity of the differential fluorescent staining method was 91.6% and the Gram stain 75.8%. The PPV and the NPV of the differential fluorescent staining method were 67.6% and 98.8% respectively and those of the Gram stain 35.9% and 92.3%.	Blinding, age of patients, reason for hospitalisation or outpatient visit are all unknown. 'Sterile technique' is not enough information about the urine collection method. Blinding reported between gram-stain and fluorescent preparation, but unknown whether blinding against the reference standard

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Winkens R;Nelissen-Arets H;Stobbering h E; 2003 [162]	Evidence Level: II	Assess validity of urine dipslides as performed under daily practice conditions and assessed the influence of the incubation period (24 v 48 hours) on validity	232 patients with 268 episodes of UTI. 83% female, 17% male. Study on the validity of the dipslide performed and judged in general practice under 'non-optimal' conditions.	Patients aged 12 years or older presenting to general practice with a median age of 54 years (range 9-93 years). Five General Practices (16 GPs) all within the same region.	Nitrite test, dipslide and culture were performed. Dipslides with at least 10^5 cfu/ml were considered to reflect a UTI.	The nitrite tests was the initial test in all practices. Of the 268 urine samples a sensitivity of 42% (95%CI 34 to 49%) and a specificity of 95% (95%CI 89 to 98%). The PPV was 93% (95%CI 85 to 98%) and the NPV 50% (95%CI 42 to 57%). The sensitivity of the dipslide in general practice after 24 hours incubation was 73% (95%CI 66 to 80%) and specificity was 94% (95%CI 88 to 98%). The PPV was 95% (95%CI 90 to 98%) and the NPV 68% (95%CI 60 to 76%). As the dipslide is only recommended in the case of a negative nitrite test, when performed after a negative nitrite test the PPV was 92% (95%CI 84 to 98%) and the NPV 73% (95%CI 64 to 81%). Overall the dipslide read under practice conditions performed lower than under optimal conditions.	Blinding unknown.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Scarparo C;Piccoli P;Ricordi P;Scagnelli M; 2002 Jun [163]	Laboratory study Evidence Level: III	To evaluate the UTI diagnostic performance of the DipStreak device with two different chromogenic medium configurations and to compare the performance to that of the reference streak method (calibrated loop).	2000 routine urine samples. 1707 Clean-catch and 262 from indwelling catheter.	876 samples collected from outpatients department and 1124 collected from patients in different departments of the hospital: 161 from Nephrology and kidney transplant unit, 137 from haematology, 101 from geriatrics, 97 from paediatrics, 92 from metabolic diseases, 90 from obstetrics and gynaegology, 89 from intensive care, 82 from urology, 80 from internal medicine, 62 from surgery and 133 from other departments.	Dipstreak device with two different medium formulations - CHROMagar and MacConkey media in one and UriSelect 3 and MacConkey in the other.	In the study comparing Dipstreak (CHROMagar and MacConkey media), Dipstreak (Uriselect 3 and MacConkey media), Uriselect 3 plates and calibrated loop culture, 2000 urine samples were processed and 511 cultures were found to be positive. The CHR dipstreak device, the Uriselect 3 and calibrated loop cultures gave the same detection rate (99.7%). For the direct identification of *E.coli*, *Proteus* and *Enterococcus* isolates, the DipStreak device and Uriselect showed overall sensitivities of 97% and 93.4%. In the second study comparing Dipstreak (Uriselect 3 and MacConkey media), Uriselect 3 plates and calibrated loop culture, 3000 urine samples were processed and 714 cultures were found to be positive. The DipStreak device, the Uriselect 3 and calibrated loop cultures gave detection rates of 99.4%, 99.9% and 99.2% respectively. For the direct identification of *E.coli*, *Proteus* and *Enterococcus* isolates, the DipStreak device and Uriselect plates showed overall sensitivities of 88.7% and 94.4% respectively	Unspecified patient population No information about blinding. Indwelling catheter, urology and intensive care patients are excluded from the scope. Patients are likely not to be representative of the paediatric population having first line urine tests for suspected UTI.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Huicho L;Campos-Sanchez M;Alamo C; 2002 [164]	Systematic review Evidence level: III	Four aims 1. Summarise the literature on urine screening tests 2. Recall the validity and applicability of the included studies. 3. Perform meta-analysis 4. Identify the test or combination of tests that best predicts the presence or absence of UTI in children..	48 articles evaluated	Children aged 0 to 18 years. Article inclusion criteria: 1. Addressing the usefulness of urinary screening tests in the diagnosis of UTI in children 0-18 years. 2. Original articles. Review papers and letters were excluded. 3. Studies in humans 4. Articles with enough information provided to judge their methodologic quality. 5. Articles with index tests and reference standard (culture) systematically performed in all patients with specification of the sampling technique. 6. Articles with prevalence, sensitivity, specificity, predictive values explicitly stated, or with data	Various urine screening tests compared to culture. Leukocyturia (or pyuria) in uncentrifuged urine. Bacteria and/or leukocytes in uncentrifuged, stained, or unstained urine. Dipstick tests (LE and Nitrite, alone or in combination)	Rapid dipstick tests could not be definitively assessed because of the small number of studies assessing their effectiveness. Bivariate SROC curves showed that pyuria ≥10/hpf and bacteriuria ≥10/hpf had the best diagnostic performance. In multivariate analysis, both remained significant	Quality of primary studies was variable. They grouped together tests which had different cut-off points. Not a particularly helpful study - does not report range of sensitivities/specificities for different tests.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
				presented in such a way that calculation is feasible. 7. Studies that were performed at a hospital or outpatient clinic with medical supervision. Studies performed at home were excluded.			

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Wiwanitkit V;Udomsantisuk N;Boonchalermvichian C; 2005 [165]	Diagnostic Laboratory study Evidence Level: Ib	Evaluate the diagnostic properties of urine Gram stain and urine microscopic examination for screening UTI and to perform additional cost-utility analysis..	95 urine samples	Samples from suspected UTI cases sent to a University microbiology department. Gram stain was considered positive if presence of ≥1 bacteria/field (x1000). Microscopy was considered positive if the presence of bacteria and pyuria >5 white blood cells or white blood cell clumps/field objective (x400). Urine culture was considered positive if 10^5cfu/ml were present	Gram stain Microscopy compared to culture.	The prevalence of UTI from culture was 54.7% (52 cases). The sensitivity of the Gram stain was 96.2%, specificity 93.0%, positive predictive value 94.3% and negative predictive value 95.2%. False positive was 7.0% and false negative was 3.8%. The sensitivity of the microscopic examination was 65.4%, specificity 74.4%, positive predictive value 75.6% and negative predictive value 64.0%. False positive was 25.6% and false negative was 34.6%. Combining the Gram stain and the microscopic examination, the sensitivity of the was 98.1%, specificity 74.4%, positive predictive value 82.3% and negative predictive value 97.0%. False positive was 25.6% and false negative was 1.9%.	Good information about blinding. Total number of subjects was small. No information about patients (age, gender etc).

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Novak R;Powell K;Christopher N; 2004 May [166]	Evidence Level: II	To determine which urine testing method best identifies UTI in children presenting to a paediatric emergency department.	142 children, 48 boys and 94 girls.	Febrile children under 5 years old who had urine samples collected by catheterisation in an Emergency department. Half of the children were ≤12 months. Samples were transported by pneumatic tube and were analysed within 60 minutes. A positive urine culture was defined as $>10^3$ colonies of a single organism.	Culture Dipstick Sediment examination Unspun leukocyte counts Cyto-centrifuge gram stain	25 cases (17.6%) of UTI were diagnosed by culture, 48% were ≤12 months and 16% were male. Positive leukocyte esterase dipstick had an overall sensitivity of 48% and a negative predictive value of 90%. In children ≤12 months, sensitivity was 42% while in children over 12 months, sensitivity was 53%. Positive nitrite dipstick had an overall sensitivity of 20% and a negative predictive value of 85%. In children ≤12 months, sensitivity was 17% while in children over 12 months, sensitivity was 23%. Positive blood dipstick had an overall sensitivity of 44% and a negative predictive value of 88%. In children ≤12 months, sensitivity was 33% while in children over 12 months, sensitivity was 53%. Positive unspun leukocyte count >10/µl had an overall sensitivity of 68% and a negative predictive value of 92%. In children ≤12 months, sensitivity was 67% while in children over 12 months, sensitivity was 69%. Positive cyto-centrifuge Gram stain had an overall sensitivity of 60% and a negative predictive value of 92%. There was a statistically	No information about blinding.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
						significant differences between children ≤12 months (sensitivity 42%) and children over 12 months (sensitivity 76%) ($p<0.05$). 2 to 5 or more leukocytes/hpf in sediment had an overall sensitivity of 48% and a negative predictive value of 90%. In children ≤12 months, sensitivity was 42% while in children over 12 months, sensitivity was 53%.	

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Al-Daghistani HI;bdel-Dayem M; 2002 Oct [167]	Evidence Level: III	To compare the performance of leukocyte esterase and nitrite dipstick with the assessment of pyuria by HPF microscopic examination and culture of urine samples in patients with symptoms of UTI.	504 patients, 271 female and 233 male	Patients presenting to a medical centre with signs and symptoms of a UTI. Urine was collected by mid-stream clean-catch.	Dipstick (nitrite and leukocyte esterase) compared to microscopy and culture.	The sensitivity of the leukocyte esterase dipstick was 68.4%, specificity 73.4%, positive predictive value 43.7% and negative predictive value 88.5%. The sensitivity of the nitrite dipstick was 58.9%, specificity 77.8%, positive predictive value 60% and negative predictive value 86.2%. The sensitivity of the microscopic pyuria count was 34%, specificity 86.5%, positive predictive value 43.5% and negative predictive value 81.3%. There was a significant correlation between dipstick results, microscopic examination and urine culture (p=0.0001).	No indication of blinding, no indication of age of patients, or exclusion criteria applied.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Arslan S;Caksen H;Rastgeldi L;Uner A;Oner AF;Odabas D; 2002 Mar [168]	Evidence Level: III	To determine the validity of the urinary Gram stain compared with a combination of pyuria plus Gram stain and overall urinalysis..	100 children	Children aged 2 days to 15 years (majority under 5 years) admitted to a Paediatric department between Jan and June 1999 with symptoms suggesting UTI. Inclusion criteria; for infants, fever with no apparent source, vomiting, decreased appetite and irritability; for toddlers, abdominal pain and voiding frequency with or without fever; and for older children, dysuria, frequency, urgency and abdominal/flank pain with or without fever. Children receiving antibiotic therapy were excluded. In infants a bag specimen was used, and in toilet-trained children a mid-stream urine sample was used.	Four tests within the urinalysis (leukocyte esterase, nitrite, microscopy for bacteria, and microscopy for pyuria), urinary Gram stain and urine culture. Complete blood count, peripheral blood smear and ESR were also analysed.	Of the 100 children, 70% had a positive urine culture. The sensitivity of the Gram stain was 80%, specificity 83%, positive predictive value 91% and negative predictive value 64%. The sensitivity of the combination of Gram stain and pyuria was 42%, specificity 90%, positive predictive value 90% and negative predictive value 40%. The sensitivity of the overall urinalysis was 74%, specificity 3.5%, positive predictive value 64% and negative predictive value 5%.	No information about blinding Did use a reference standard, but unclear description (used 'overall urinalysis' which included culture).

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
				Cultures were considered positive if the culture showed greater than 100,000 colonies of a single pathogen. Pyuria was considered present if more than 5 WBCs were noted on unstained microscopy and bacteriuria if at least a 'slight' reading was noted at 40x/hpf.			

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Manoni F;Valverde S;Antico F;Salvadego MM;Giacomini A;Gessoni G; 2002 Oct [169]	Diagnostic Evidence Level: II	Evaluation of the analytical performance of the Sysmex UF-100 cytometer compared to the diagnosis of UTI.	2010 patients	Patients aged between 18 and 78 years (mean 56.4 years) with urine sample submitted to a lab. 1130 (496 males and 634 females) were outpatients and 880 (374 males and 506 females) were inpatients. The majority (90%) of samples were voided urine specimens.	Chemical and physical examination of urine specimen. Dipstick analysis included reagent pads for semi-quantitative assessment of relative density, pH, leukocyte esterase, nitrite, protein, glucose, keytones, urobilinogen, bilirubin and haemoglobin. Microscopic examination Each specimen was centrifuged at 400g for 10 mins. In each specimen at least 20 random microscopic fields were examined at x400 HPF. Culture Samples were inoculated on agar plates by using 0.001ml calibrated loops within 4 hours. After 24 hours cultures were qualified in CLED plates. UF-100 The Sysmex UF-100 is a second-generation automated urine analyser that performs analysis of the formed elements in urine by flow cytometry.	Of the 2010 patients considered, 529 (26.3%) had a UTI. Of the dipstick screening tests (Nitrite and leukocyte esterase dipstick tests) 171 (8.5%) false negatives were observed and 184 (9.2%) false positives. Sensitivity was 0.64 and specificity of 0.88 while PPV was 0.63 and NPV was 0.89. Of the culture tests (bacterial growth on CLED agar) 56 (2.8%) false negatives were observed and 35 (1.7%) false positives sensitivity was 0.89 and specificity of 0.98 while PPV was 0.93 and NPV was 0.89. Of the UF-100 tests 29 (1.4%) false negatives were observed and 102 (5.1%) false positives. Sensitivity was 0.94 and specificity of 0.93 while PPV was 0.83 and NPV was 0.98. The sysmex UF-100 performed more accurately than both the dipstick testing and culture.	No information about blinding to the reference standard

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Reilly P;Mills L;Bessmer D;Jimenez C;Simpson P;Burton M; 2002 [170]	Diagnostic Evidence Level: III	: To determine if the biochemical results of the urine dipstick could be used to eliminate unnecessary urine cultures	Part One: 843 urine samples Part Two: 6192 urine samples	Urine samples sent to a laboratory for culture. Part one: involved a 3 month retrospective review on urine samples that had both dipstick and culture ordered. Part two: implementation of a policy to screen urine samples having both urinalysis and culture ordered to determine the number of unnecessary urine cultures sent to the lab.	Dipstick compared to culture.	Of the 6192 urine samples processed, 64% (3932) had cultures performed. These were samples which showed positive dipstick and were ordered on physician request, or were not cancelled. 36% (2260) had a negative dipstick and were cancelled. The rate of cancellation appeared consistent at approximately one third when tracked month by month. Of the 3932 samples cultured 22.4% (883) were true positives (positive dipstick and positive culture), while 31.8% (1248) had a positive dipstick but grew organisms that were considered contaminants. False positive results were observed in 1558 (39.6%). Of the samples that showed negative dipstick and were cultured 11 (0.3%) grew a clinically significant pathogen. The study concluded that the biochemical parameters on urine dipsticks can be used as a screen to determine whether or not a urine culture should be performed and implementation of this policy has resulted in the elimination of up to one third of the urine cultures performed in one laboratory	Unsure of the biases in this study -

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Smith P;Morris A;Reller LB; 2003 Apr [171]	Diagnostic Evidence Level: III	To determine whether dipstick or microscopy results reliably predict the presence or absence of a reportable urinary pathogen in an effort to develop practical options to increase the proportion of urine cultures with clinically useful results..	500 urine specimens from patients aged 1 month to 91 years (median 44 years). 60 (12%) in patients aged under 14 years. 336 (67%) from females.	All clean-catch, mid-stream urine samples, or those obtained by single catheterisation were included if they were received by the lab within 10 hours of collection. Patients with indwelling catheters were excluded. Samples were considered positive at 10^5 cfu/ml Pyuria was defined by microscopy as ≥10WBC/mm^3 Contamination was defined as ≥10 squamous epithelial cells/mm^3	The presence of leukocyte esterase and urinary nitrite was determined using dipstick (Chemstrip 2 LN dipsticks). Following this, the presence of WBCs, RBCs and squamous epithelial cells was determined by microscocopy at 100x and 400x magnification.	There were 266/500 (53%) specimens with no growth and 77 (15%) had pure growth of a pathogen. The sensitivity of detecting pyuria on microscopy to predict the presence of a pathogen was 63%, specificity 89%, positive predictive value 58% and negative predictive value 91%. The sensitivity of detecting haematuria on microscopy to predict the presence of a pathogen was 18%, specificity 89%, positive predictive value 27% and negative predictive value 82%. The sensitivity of detecting squamous epithelial cell (SEC) contamination on microscopy to predict mixed culture was 34%, specificity 89%, positive predictive value 53% and negative predictive value 78%. The sensitivity of detecting negative microscopy (no WBCs or SECs) to predict the absence of a pathogen was 76%, specificity 74%, positive predictive value 92% and negative predictive value 74%. The sensitivity of a negative dipstick to predict the absence of a pathogen was 83%, specificity 76%, positive predictive value 94% and negative predictive value 76%. The sensitivity of a	No information about blinding Not in an appropriate spectrum of patients - aged 1 month to 91 years.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
						negative dipstick and negative microscopy to predict the absence of a pathogen was 68%, specificity 85%, positive predictive value 95% and negative predictive value 85%. Overall, the presence of haematuria or SECs were poor predictor of specimens with mixed cultures. The absence of pyuria had a reasonable negative predictive value (91%) for the presence of a pathogen. Negative microscopy had an adequate positive predictive value (92%), as did negative dipstick (94%). The combination of negative microscopy and dipstick (95%) did not significantly increase the ability to detect a pathogen.	

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Bachur R;Harper MB; 2001 [172]	Retrospective medical record review Evidence Level: III	To determine how the sensitivity of the standard urinalysis as a screening test for UTI varies with age and to determine the clinical situation that necessitates the collection of urine culture regardless of the urinalysis result..	37450 children (44% girls) 11089 patients with urine cultures obtained	Children younger than 2 years with fever (≥38°C) seen in an emergency department during a period of 65 months. Cultures were considered positive if $\geq 10^3$ cfu/cl for supra-pubic aspiration, $\geq 10^4$ fo catheterised specimens and $\geq 10^5$ for clean voided specimens. Contaminated specimens were excluded.	All cultures were reviewed for the collection method, isolates and colony units. A urinalysis was considered positive if the presence of one of the following was detected: leukocyte esterase, nitrite, or pyuria.	One study investigated the sensitivity of the standard urinalysis as a screening test for UTI to determine how it varies with age and to determine the clinical situation that necessitates the collection of urine culture regardless of the urinalysis result. The study found that sensitivity of urinalysis was 82% (95%CI 79-84%) and did not vary with age. The specificity of urinalysis was 92% (95%CI 91-92%). The positive likelihood ratios was 10.6 (95%CI 10.0 to 11.2) and the negative likelihood ratio was 0.19 (95%CI 0.18 to 0.20).	Large sample size, although retrospective design does not allow interpretation of why not all patients tested with the reference standard (culture). Blinding not described.

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2

Clinical features of UTI

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Pecile P;Miorin E;Romanello C;Falleti E;Valent F;Giacomuzzi F;Tenore A; 2004 Aug [174]	Study type: Diagnostic Evidence level: II	To determine the accuracy of procalcitonin measurements in diagnosing acute renal involvement during febrile UTI and in predicting subsequent scars as assessed with DMSA.	100 consecutive children (69 girls and 31 boys) admitted to a peaediatric department between Jan 2000 and Jan 2002 with first episode of febrile UTI	Children 1 months to 13 years (mean 19 months). 66 children were under 1 year. Definition of UTI was positive culture with a single microorganism at ≥10^5cfu/ml from a catheterised or clean voided sample. Patients with previously documented or suspected febrile UTIs were excluded	CRP levels, procalcitonin levels, ESR and leukocyte counts compared to DMSA	Clinical and Laboratory assessments - body temperature - duration of fever - WBC count - CRP level (values of ≥20mg/l were considered abnormal) - ESR - procalcitonin level (values of ≥0.8ng/ml were considered abnormal) Imaging studies - Ultrasound (performed within 3 days) - VCUG (1 month after first infection to detect reflux) - DMSA (5 days after admission). Score of 0 = absence of lesion, 1=uncertain or mild lesion, 2=mild lesion, 3=moderate lesion, 4=severe renal parenchymal lesion (covering >30% of surface area).	Study only showed diagnostic accuracy for the group of patients who scored 2-4 indicating acute pyelonephritis – more significant initial renal damage. The diagnostic accuracy for the group with mild renal damage is unknown. Additionally, only children who scored 2-4 were followed up.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Lin DS;Huang SH;Lin CC;Tung YC;Huang TT;Chiu NC;Koa HA;Hung HY;Hsu CH;Hsieh WS;Yang DI;Huang FY; 2000 Feb [175]	Study type: Diagnostic Evidence level: III	To assess the usefulness of laboratory parameters including peripheral WBC count, CRP, ESR and microscopic urinalysis for identifying febrile infants younger than 8 weeks of age at risk of UTI.	162 febrile children (94 boys, 68 girls)	Febrile infants (rectal temperature >38°C) under 8 weeks old who presented to an emergency department between September 1997 and August 1998 and were hospitalised. Exclusions: Infants who received antibiotics or had a SPA within 24 hours.	History and physical examination and a full evaluation for sepsis including peripheral WBC count, and differential ESR, CRP, blood culture, lumbar puncture, glucose level, protein level, Gram stain, urinalysis and culture. All urine samples were collected by SPA.	All infants had negative blood and CSF cultures. 22/162 (13.6%) had positive urine cultures (4 girls, 18 boys). Hemocytometer WBC counts (≥10 WBC/μl) Sensitivity: 82% Specificity: 94% Accuracy: 92% LR+: 12.7 LR-: 0.19 Standard UA (≥5 WBC/hpf) Sensitivity: 59% Specificity: 93% Accuracy: 88% LR+: 8.3 LR-: 0.44 CRP (>20 mg/L) Sensitivity: 59% Specificity: 90% Accuracy: 86% LR+: 5.9 LR-: 0.45 ESR (>30 mm/h) Sensitivity: 73% Specificity: 78% Accuracy: 77% LR+: 3.3 LR-: 0.35	

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
						Peripheral WBC (>15000/µl) Sensitivity: 36% Specificity: 80% Accuracy: 74% LR+: 1.8 LR-: 0.80	

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Benador N;Siegrist CA;Gendrel D;Greder C;Benador D;Assicot M;Bohuon C;Girardin E; 1998 Dec [176]	Study type: Diagnostic Evidence level: III	To measure PCT levels in children with febrile UTI, to compare it to other inflammatory markers and to evaluate it's ability to predict renal involvement as assessed by DMSA.	60 children (17 boys, 43 girls)	Children 1 month to 16 years old (mean age lower UTI 36 months, mean age pyelonephritis 42 months) diagnosed with clinical signs of acute pyelonephritis. Acute pyelonephritis defined as rectal temperature ≥38°C and abdominal pain in older children, or non-specific signs in younger children such as irritability or vomiting. Confirmation by positive urine culture where ≥104cfu/ml for midstream clean voided urine, ≥103 for SPA or catheterisation.	Test: Blood samples were collected on admission for determination of PCT, CRP and leukocyte counts Tests were considered abnormal at: PCT >0.6µg/L CRP >10mg/L DMSA was performed within 5 days of admission. Lesions were graded in 5 categories: 0 – absence of lesion (lower UTI) 1 – very mild (defect covering<5% surface area) 2 – mile (defect covering 5% - 10% surface area) 3 – moderate (defect covering 10% - 30% surface area) 4 – severe renal parenchymal lesions (defect covering >30% surface area)	Age (months) – 36 ± 9 vs. 42 ± 8, p=0.350 Sex (female/male) – 14/9 vs. 29/8, p=0.140 Leukocyte count (mm3)– 10939 ± 834 vs. 17429 ± 994, p=0.0001 PCT (µg/L) – 0.38 ± 0.19 vs. 5.37 ± 1.9, p<0.0001 CRP (mg/L) – 30.3 ± 7.6 vs. 120.8 ± 8.9, p<0.0001 When inflammatory markers were correlated with severity of renal lesions ranked by DMSA, PCT was significantly correlated (p<0.0001) however CRP was of borderline significance (p=0.032). CRP Sensitivity: 100% Specificity 26.1% PCT Sensitivity: 70.3% Specificity: 82.6%	

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Gurgoze MK;Akarsu S;Yilmaz E;Godekmerdan A;Akca Z;Ciftci I;Aygun AD; 2005 [177]	Study type: Diagnostic Evidence level: III-	Compared serum levels of proinflammatory cytokines and procalcitonin in children with acute pyelonephritis and with lower tract UTI to establish whether they could be used as a marker in distinguishing acute pyelonephritis.	76 children (48 girls, 28 boys)	Children aged 2 to 144 months (mean age 39.6 ± 33.8 months). All children had been diagnosed with UTI by clinical findings (fever, nausea/vomiting, appetite, dysuria, nonspecific abdominal pain) and laboratory analysis (10^5cfu/ml midstream sample or 10^3cfu/ml in a catheterised sample).	Test: Blood sample (before initiating antibiotic treatment) DMSA Reference test:	34 children (20 girls and 14 boys) had acute pyelonephtritis (mean age 43.4 months) and 42 children (28 girls and 14 boys) had lower UTI (mean age 34.6 months). PCT (at 0.5ng/ml) Sensitivity 58% Specificity 76% CRP (at 20mg/l Sensitivity 94% Specificity 58% IL-ß1 (at 6.9pg/ml) Sensitivity 97% Specificity 59% IL-6 (at 18pg/ml) Sensitivity 88% Specificity 74% TNF-a (at 2.2pg/ml) Sensitivity 88% Specificity 80%	Study did not provide numbers so no sensitivities/specificities could be checked. Also cannot calculate PPV or NPV. Evidence level - so should be excluded if other quality studies are found.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Smolkin V;Koren A;Raz R;Colodner R;Sakran W;Halevy R; 2002 [178]	Study type: Diagnostic Evidence level: III-	To evaluate the ability of PCT level to predict renal involvement assessed by DMSA.	64 children (44 girls and 20 boys)	Children aged 2 weeks to 3 years (mean 16.7 ± 8.6 months) admitted to a paediatric department with febrile UTI. Inclusion was confirmed by a positive urine culture. Positive urine culture was defined as any growth on SPA and 10^3cfu/ml on catheterisation.	Test: Reference test: CRP and PCT (on admission) compared to DMSA (performed within 7 days of admission) PCT where a value of >0.5ug/l was considered abnormal CRP where a value of >20mg/l was considered abnormal. DMSA where renal pathology was defined as focal or multifocal perfusion defects or as split renal uptake of less than 45%.	CRP at a cut off value of 20mg/l Sensitivity 100% Specificity 18.5% PPV100% NPV 30.9% PCT at a cut off value of 0.5ug/l Sensitivity 94.1% Specificity 89.7% PPV 97.6% NPV 85.7% The median PCT level was significantly higher in the acute pyelonephritis group (3.41, range 0.36 to 12.4) than the lower UTI group (0.13 range 0.02 to 2.15) p<0.0001.	Study did not provide numbers so no sensitivities/specificities could be checked. Evidence level - so should be excluded if other quality studies are found.

1

1 Antibiotic treatment

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Dagan R;Einhorn M;Lang R;Pomeranz A;Wolach B;Miron D;Raz R;Weinstock A;Steinberger J; 1992 180	Study Type: RCT Evidence level: 1+	To compare the safety and efficacy of once daily oral cefixime to twice daily oral TMP/SMX for treating acute UTI in children.	94 children enrolled, 76 evaluated 38 received cefixime and 38 received TMP/SMX	Children aged 6 months to 13 years with symptoms of urinary tract infection (confirmed by positive culture). Positive urine defined asmore than 10^5cfu/ml from a clean catch sample, more than 10^3 from catheterisation or SPA. Exclusions: hypersensitivity to beta-lactam antibiotics, sulfa compounds or trimethoprim; children receiving antibacterial medications; children from whom a resistant organism was	Intervention: Once daily oral cefixime (8mg/kg) or. Twice daily oral TMP/SMX (8/40mg/kg/day) in divided doses. Treated for 7 to 10 days depending on standard practice within each centre. Comparison: TMP/SMX vs. cefixime.	Follow-up period: 7 to 10 days. Outcome Measures: Urine sterilisation ESR WBC count	Of the original 96 children, 9 had a negative urine culture and a further 9 were Excluded from the study because of poor compliance. Baseline characteristics were similar on enrollment. 28/76 (37%) children were under 3 years of age and one third had history of recurrent UTI. Peripheral white blood cell counts, body temperature and urianalysis returned to normal at the same rate in both groups (data presented in graphs, no numbers provided) ESR on admission Cefixime 44.7±24.6 TMP/SMX 42.4±26.5 ESR 1-2 hours post treatment Cefixime 22.5±11.5 TMP/SMX 20.8±12.8 No failures were observed and relapse occurred in 3 cases within 4 weeks after treatment.	Not enough numbers presented to check whether the calculations are correct - mostly presented as 3D figures. No blinding. 9/94 children were excluded because of poor compliance. This will have an effect on the adverse effects data, which has been omitted for this reason.

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				isolated; underlying anomalies or chronic diseases; children with more than one site of infection; frequent vopmiting not permitting oral therapy.				

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Ahmed M;Sloan JE;Clemente E; 2001 [181]	Study Type: RCT Evidence level: 1-	To determine the comparative safety and efficacy of TMP and TMP/SMX in children with uncomplicated UTI.	125 patients randomised (59 evaluated) 30 TMP 29 TMP/SMX	Children 6 months to 12 years of age (mean age 5.2±0.6 years in TMP children and 5.2±0.7 in TMP/SMX children))with bacteriologically confirmed UTI (>10^5cfu/ml) seen at an outpatients centre.	Intervention: Oral TMP (10mg/kg/day) or TMP/SMX (40mg/kg/day) administered twice daily in divided doses for 10 days. Comparison: TMP monotherapy vs. TMP/SMX combination therapy	Follow-up period: 38-42 days Outcome Measures: Urine steralisation Symptom reduction	No statistically significant differences were found between the two groups. Bacteriological outcome TMP 26/30 (86.7%) TMP/SMX 27/29 (93.1%) p=0.5546 Clinical response TMP 26/30 (86.7%) TMP/SMX 26/30 (86.7%)	Study states that the trial was multi-centre, randomised and investigator-blind, however no further details are available. 125 patients were randomised to treatment, however only 59 were evaluated. Over 50% loss to follow-up with no explanation provided.

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Howard JB;Howard JE; 1978 [182]	Study Type: RCT Evidence level: 1-	To assess the possible superiority of the combination of TMP/SMX over SMX alone in treating children with UTI.	229 children randomised, 118 evaluated 61 treated with TMP/SFX 57 treated with Sulfamethoxozole alone	Children between 6 months and 10 years with urinary tract infection who could be kept under medical observation for 42 days. Exclusions: chronic or recurrent infection	Intervention: TMP/SMX (10-12mg/kg) SMX (50 to 60mg/kg) Both given in three divided doses. Comparison: TMP/SMX vs. SMX	Follow-up period: 42 days Outcome Measures: Clinical and bacteriological cure was defined as the absence of signs and symptoms and sterile culture at 14 day follow up	Of the original 229 enrolled, 44 failed to return, in 52 the initial urine culture was negative and 15 did not take the medication. Groups were similar at baseline, however a greater number in the TMP/SMX group had fever (57% vs. 37%, $p<0.05$) There were no significant differences in responses to therapy at 10 days in terms of urine steralisation, or adverse effects.	Children were excluded continuously, reducing the power to detect a difference at each point. Started with 229, 44 failed to return, in 52 the initial urine culture was negative and 15 did not take the medication. Of the remaining 118, 16 did not keep return appointments, 2 did not take the medication, and 1 was not evaluated because of vomiting. There is no way of knowing what the effects of this had on the effectiveness of the oral antibiotics.

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Bloomfield P;Hodson EM;Craig JC; 2005 [183]	Study Type: Systematic review - meta-analysis Evidence level: 1++	To determine the benefits and harms of different antibiotic regimens for the treatment of acute pyelonephritis in children	2612 children in 18 studies 2320 (89%) were assessed for at least one outcome of effectiveness	Children aged 0-18 with proven UTI and acute pyelonephritis treated in either a hospital or outpatients with antibiotics. Diagnosis of acute pyelonephritis required culture of more than 108cfu/L with at least one symptom of systemic illness. Previously diagnosed renal tract abnormalities including VUR were included. Asymptomatic or cystitis were excluded.	Intervention: Parallel RCTs Comparison: Oral therapy vs. short duration IV therapy followed by oral therapy Short duration IV (3-4 days) followed by oral therapy vs. long duration IV The addition of a single does of IV to oral therapy Different dosing frequencies of the same antibiotic	Follow-up period: 3 weeks - 1 year Outcome Measures: Persistent bacteriuria at 48-72 hours. Resolution of clinical symptoms Parenchymal renal damage (on DMSA) Adverse effects	1. Oral therapy vs. IV Time to fever resolution WMD 1.54 (-1.67 to 4.76) Rate of symptomatic recurrence RR 0.67(0.27, 1.67) Rate (RR 1.45 (0.63, 3.03))or size (RR -0.70 (-1.74, 0.34))of renal parenchymal defect on DMSA at 6 months. 2. Short vs. Long duration IV Recurrent UTI within 6-12 months, four trials (RR 1.15 (0.52, 2.51)) Persisting renal parenchymal defects seen on DMSA at 3-6 months, three trials (RR 0.99 (0.72, 1.37)) Adverse effects - gastrointestinal upset (RR 1.29 (0.55, 3.05)) 3. Single dose parenteral and oral vs. oral alone Persistence of bacteriuria (RR 0.77 (0.19, 3.20)) Persistence of clinical symptoms (RR 0.82 (0.24, 2.81)) Total adverse effects (RR 1.37 (0.33, 5.68)) 4. Different dosing regimens Daily parenteral gentamicin or netilmicin v. 8 hour administration. Persisting bacteriuria at 1-3 days(RR 1.98 (0.37, 10.53)) Persisting clinical symptoms (RR 1.98 (0.37, 10.53))	Quality of included studies was variable with larger, more recent trials having adequate quality.

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
							Persisting bacteriuria at one week (RR 2.48 (0.12, 68.57)) Recurrent UTI within 1 month (RR 1.18 (0.33, 4.23)) Time to fever resolution (WMD 2.40 (7.92, 12.72)) 5. Different IV antibiotics IV cefipime to IV ceftazidime: 1 trial involving 299 children (Ref ID 211). There were no significant differences between the groups for bacteriuria (RR 0.12 95%CI 0.01 to 2.16), recurrent infection (RR 0.68 95%CI 0.45 to 3.18), occurrence of unsatisfactory clinical response (RR 0.68 95%CI 0.12 to 4.02) or adverse events (RR 1.41 95%CI 0.65 to 3.07). 6.IV cefotaxime to IV amoxicillin/clavulanic acid: 1 trial involving 20 children (Ref ID 138). Two children treated with cefotaxime but none treated with amoxicillin/clavulanic acid had persistent bacteriuria at 48 hours (RR 5.50 95%CI 0.30 to 101.28). Two children treated with cefotaxime but none treated with amoxicillin/clavulanic acid had persistent fever at 48 hours(RR 5.00 95%CI 0.27 to 92.62). Three children treated with amoxicillin/clavulanic but none treated with cefotaxime had gastrointestinal adverse effects (RR 0.14 95%CI 0.01 to 2.45). IV cefotaxime to IV ceftrixone: 1 trial involving	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
							100 children over the age of 24 months (Ref ID 111). There was no significant difference between the groups for bacteriuria (none in either group after 48h), recurrent infection (RR 0.87, 95%CI 0.37 to 2.03 at one month and RR 0.68, 95%CI 0.30 to 1.50) or adverse events (RR 0.67, 95%CI 0.12 to 3.82). aminoglycosides IV isepamicin to IV amikacin: 1 trial involving 16 children compared the (Ref ID 159). There were no significant differences between the groups for bacteriuria (no patient in either group had persistence of bacteriuria after 48 h, 7 days or 30 days) or resolution of fever (mean time same in each group 24h). 7. Single dose vs. longer duration of oral (2 studies) Persistence of bacteriuria (RR 1.73 (0.18, 16.30)) Recurrent UTI with in 6 weeks (RR 0.24 (0.03, 1.97))	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Fischbach M;Simeoni U;Mengus L;Jehl F;Montei l H;Geiser t J;Janin A; 1989 184	Study Type: RCT Included in Cochrane review (Ref ID 87) Evidence level: 1+	To compare the efficacy and tolerance of two treatment regimens with tissue penetratio n	Total 20 participants 10 treated with IV cefotaxime 10 treated with IV amoxycillin /clavulanate	Children above the age of 1 year with urinary tract infection (urinary leukocyte count greater than 10 white blood cell /mm^3 and a bacteriuria greater than or equal to 100,000 colonies/ml, a predominant isolate (more than 80% of the flora), with tissue penetration shown both clinically (poor general condition, lumbar or abdominal pain, temperature above 38.5ºC) and on laboratory tests (ESR greater than 35mm at 1 hour, elevated CRP and orosomucoid)). Children	Intervention: IV cefotaxime 100mg/kg/day in 4 infusions over 30 min for 14 days versus IV amoxycillin /clavulanate 100mg/kg/day in 4 infusions over 30 min for 7 days followed by oral amoxycillin /clavulanate 50mg/kg/day for 7 days Comparison: treatment vs treatment	Follow-up period: unknown Outcome Measures: Time to defervescence (hours) Sterilization of the urine (0 bacteria/ml)	Time to defervescence ≤ 36 hours: cefotaxime 4/10, amoxycillin /clavulanate 5/10 36-48 hours: cefotaxime 4/10, amoxycillin /clavulanatev 5/10 > 48 hours: cefotaxime 2/10, amoxycillin /clavulanate 0/10 Sterilization of the urine ≤ 48 hours: cefotaxime 7/10, amoxycillin /clavulanate 10/10 48-72 hours: cefotaxime 2/10, amoxycillin /clavulanate 0/10 not obtained: cefotaxime 1/10, amoxycillin /clavulanate 0/10	Small number of participants

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				excluded from the study: definite or suspected allergy to β-lactams, antibiotic therapy within the 72h before inclusion in the trial, impaired renal function or post operative infections. 3 participants had a history of congenital abnormalities, 4 has a history of pyelonephritis				

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Schaad UB;Esko la J;Kafetzi s D;Fishba ch M;Ashke nazi S;Syriop oulou V;Boules teix J;De P;Gres JJ;Rollin C; 1998[185]	Study Type: RCT Included in Cochrane review (Ref ID 87) Evidence level: 1+	To compare the safety and efficacy of cefepime compared to ceftazidim e for treating pyelonephr itis in children younger than 12 years old.	Total 299 patients 149 in cefepime group 150 in ceftazidime group	≥ 1 month and ≤ 2 years weight at least 3 kg infection requiring hospitalisation, fever at least 38.5 ºC, white blood cell count > 15000 per ml, evidence of pyuria	IV cefepime 50 mg/kg every 8 hours versus IV ceftazidime 50 mg/kg every 8 hours continued until at least 48 hours after having become afebrile, then IV treatment continued or replaced with oral antibiotic therapy (trimethoprim-sulfamethoxazole)	Follow-up period: Follow up at 5-9 days and 4-6 weeks after end of total therapy Outcome measures: Persistent bacteriuria and unsatisfactory clinical response at end of IV therapy and end of antibiotic therapy Recurrent UTI and unsatisfactory clinical response at 5-9 days and 4-6 weeks after end of therapy Adverse effects	Persistence or recurrence of initial pathogen: at end of IV therapy, cefepime 1/111 versus ceftazidine 0/113 (RR 3.05, 95%CI 0.13, 74.16) at end of antibiotic therapy, cefepime 0/96 versus ceftazidine 4/102 (RR 0.12, 95%CI 0.01, 2.16) at 5-9 days after treatment, cefepime 5/95 versus ceftazidine 2/91 (RR 2.37, 95%CI 0.47, 11.91) at 4-6 weeks after treatment, cefepime 1/91 versus ceftazidine 8/97 (RR 0.13, 95%CI 0.02, 1.04) Infection with new pathogen: at 4-6 weeks, cefepime 8/115 versus ceftazidine 7/120 (RR 1.19, 95%CI 0.45, 3.18) Unsatisfactory clinical response: at end of IV therapy, cefepime 2/115 versus ceftazidine 3/118 (RR 0.68, 95%CI 0.12, 4.02) at end of antibiotic therapy, cefepime 2/100 versus ceftazidine 0/102 (RR 5.10, 95%CI 0.25, 104.90) at 5-9 days after treatment, cefepime 2/99 versus ceftazidine 0/100 (RR 5.05, 95%CI 0.25, 103.87) at 4-6 weeks after treatment, cefepime 2/95 versus ceftazidine 8/105 (RR 0.28, 95%CI 0.06, 1.27)	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
							Adverse effects: total, cefepime 41/149 versus ceftazidine 37/150 (RR 1.12, 95%CI 0.75, 1.63) drug-related, cefepime 14/149 versus ceftazidine 10/150 (RR 1.41, 95%CI 0.65, 3.07) gastrointestinal, cefepime 10/149 versus ceftazidine 9/150 (RR 1.12, 95%CI 0.47, 2.67) cutaneous, cefepime 3/149 versus ceftazidine 2/150 (RR 1.51, 95%CI 0.26, 8.91) discontinuation due to drug related adverse effects, cefepime 4/149 versus ceftazidine 1/150 (RR 4.03, 95%CI 0.46, 35.61)	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Bakkaloglu A;Saatci U;Soylemezoglu O;Ozen S;Topaloglu R;Besbas N;Saatci I; 1996 186	Study Type: RCT Included in Cochrane review (Ref ID 87) Evidence level: 1+	To compare the efficacy of ceftriaxone and cefotaxime in childhood pyelonephritis	100 children 50 (38 girls and 12 boys) received ceftriaxone 50 (40 girls and 10 boys) received cefotaxime	Children aged 2 to 14 with complicated or uncomplicated pyelonephritis Pyelonephritis was defined as symptoms and culture showing 10(5) cfu	Intervention: IV Ceftriaxone (50mg/kg once daily) or IV cefotaxime (50mg/kg twice daily) for 10 days Comparison: Treatment vs. treatment	Follow-up period: 4-5 weeks Outcome Measures: Urine steralisation Symptom resolution	Baseline characteristics were similar between groups. 45 children had pathological findings on radiological assessment (abdominal ultrasound, IVU and VCUG), 48 in the ceftriaxone group and 42 in the cefotaxime group and were defined as complicated cases. VUR 17 Hydronephrosis 5 Urolithiasis 5 Pelvicalyceal ectasia in 8 Bladder diverticula 4 Other abnormalities 6 Urine sterilisation at 10 days post-treatment Ceftriaxone 42/50 (84%) Cefotaxime 41/50 (82%) Urine sterilisation at 10 days post-treatment Ceftriaxone 42/50 (84%) Cefotaxime 39/50 (78%) Adverse effects in the ceftriaxone group were increased transaminase ALT in one patient, allergic cutaneous reaction in one patient and diarrhea in one patient.. Adverse effects in the cefotaxime group were increased transaminase ALT in one patient and AST in one patient and skin eruptions in three patients.	Results are reported of 'overall efficacy' however numbers in table don't relate to the 10 day or 28 day cure rates. For this reason results reported here include 10 day and 28 day data separately.

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Kafetzis DA;Maltezou HC;Mavrikou M;Siafas C;Paraskakis I;Delis D;Bartsokas C; 2000 187	Study Type: RCT Included in Cochrane review (Ref ID 87) Evidence level: 1+	To compare the efficacy and safety of isepamicin with amikacin in the treatment of paediatric patients with acute pyelonephritis and to compare blood levels in paediatric patients after administration of the same dosage.	Total 16 patients 10 in isepamicin group 6 in amikacin group	16 patients (10 girls and 6 boys) 10 in isepamicin group 6 in amikacin group Mean age 3 months, range 1 to 84 months. Acute pyelonethritis (fever > 38ºC, and according to age, refusal to feed, vomiting, abdominal pain, lethargy or focal genitourinary signs in a child with laboratory signs of pyuria, leukocytosis, increased C-reactive protein (> 30 mg/ml) an increased erythrocyte sedimentation rate and the isolation of a bacterial pathogen from two samples of	Intervention: IV isepamicin versus IV amikacin 7.5mg/kg bd infusion lasting 30 min, for 10-14 days. Administered solely or in combination with an appropriate antimicrobial agent Comparison: treatment vs treatment	Follow-up period: 30 days following completion of treatment Outcome Measures: Clinical response defined as cure, improvement or failure Relapse defined as reappearance of signs and symptoms of infection following their initial resolution Bacteriological response constituted the primary efficacy endpoint and was defined as either elimination or persistence of the causative pathogen in urine culture. Superinfection was defined as isolation of additional	Clinical response defined as cure isepamicin 9/10, amikacin 6/6 elimination of the causative agent but not cure isepamicin 1/10, amikacin 0/6 Relapse - isepamicin 0/10, amikacin 0/6 Bacteriological response pathogens isolated from blood or urine culture - isepamicin 0/10, amikacin 0/6 Superinfection - isepamicin 0/10, amikacin 0/6 Adverse effects - no clinical or laboratory adverse events complicated the course of any patient.	Small number of participants, no power calculation

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				clean catch urine at ≥ 100,000 colony-forming units/ml or ≥ 100 colony-forming units/ml from a urine sample obtained by suprapubic aspiration or urethral catheterization before treatment) Patients excluded if they received any antibacterial treatment within four weeks prior to study initiation, a history of intolerance to any aminoglycoside, impaired baseline renal, hearing or vestibular function or were infected with a pathogen resistant to		pathogens in repeated urine culture. Adverse effects, graded as mild, moderate, severe, or life-threatening.		

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				aminoglycosides. Underling disease: 2 patients with hydronephrosisin (one in association with left ureteral stenosis), 1 patient with left double renal pelvis, 1 patient withgrade II vesicourethral reflux and 1 patient with bronchiolitis				

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Vilaichone A;Watana D;Chaiwatanarat T; 2001 188	Study Type: RCT Included in Cochrane review (Ref ID 87) Evidence level: 1+	Efficicay of treatment for long term outcomes	Total 36 participants 18 in IV ceftriaxone switch to oral ceftibuten group 18 in 10 day IV ceftriaxone group	Age 1 month to 15 years Acute pyelonephritus, 1) fever of more than 38ºC or subnormal temperature in small infants, 2) pyuria (WBC ≥ 5/high power field) and/or bacteriuria (≥ 1 gram negative rod per 10 oil immersion fields in a gramstained uncentrifuged urine), 3) positive urine culture (more than 10000 colony forming unit/cc, single pathogen on midstream clean catch or bag urine) 4) 99mTc-DMSA scan demonstrated cortical defect. Exclusions: age < 1 month,	Intervention: IV ceftriaxone 75mg/kg/day after 24-48 hours after defervescence switched to oral ceftibuten 9 mg/kg/day total duration 10 days (patients discharged after switching to oral antibiotics) versus IV ceftriaxone 75mg/kg/day for 10 days Comparison: short duration IV treatment vs 10 day IV treatment	Follow-up period: 6 months Outcome Measures: Abnormal DMSA at 6 months Recurrent UTI during 6 months Persistent bacteriuria at end of treatment Adverse effects	Abnormal DMSA at 6 months: 12/18 vs 11/18, RR 1.09 95% CI 0.67, 1.79 Recurrent UTI during 6 months: 2/18 vs 1/18, RR 2.00 95% CI 0.20, 20.15 Persistent bacteriuria at end of treatment: 0/18 vs 0/18 Adverse effects: 1/18 vs 0/18, RR 3.00 95% CI 0.13, 69.09	Small study

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				previous UTI, unknown uropathy, allergic to trial antibiotics, renal failure, chronic disease, antibiotics in previous 48 hours				

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Benador D;Neuhaus TJ;Papazyan J;Willi UV;Engel-Bicik I;Nadal D;Slosman D;Mermillod B;Girardin E; 2001 189	Study Type: RCT Included in Cochrane review (Ref ID 87) Evidence level: 1+	To compare th prevalence of scarring following initial treatment with antibiotics administered intravenously for 10 or 3 days.	435 children randomised (217 in 3 day IV group and 218 in 10 day IV therapy group) 209 found not to fulfill study criteria (106 in 3 day group and 100 in 10 day) 9 patients dropped out at request of parents (217 in 3 day group and 218 in 10 day)	Age 3 months to 16 years. Mean age younger in 10 day IV therapy group: 1.0 years (range 0.5-3.3) vs 2.4 years (range 0.8-5.6) all other base line characteristics similar. With probable acute pyelonephritis. Exclusion criteria: Age < 3months, history of urinary abnormalities of and hypersensitivity to cephalosporins Randomisation occured before final enrolment, which required a positive initial urine culture and a first scintigraphy	Intervention: 3 days IV ceftriaxone 50 mg/kg once daily then 12 days oral cefixime 4 mg/kg twice daily versus 10 days IV ceftriaxone 50 mg/kg once daily then 5 days oral cefixime 4 mg/kg twice daily. At end of treatment all given prophylaxis with co-trimoxazole. Comparison: 3 day IV treatment vs 10 day IV treatment	Follow-up period: 3 months Outcome Measures: Scaring on DMSA at 3 months Recurrent UTI at 3 months	Scaring on DMSA: 9/110 vs 6/110 RR 1.50 95% CI 0.55, 4.07 Recurrent UTI: 40/110 vs 36/110 RR 1.11 95% CI 0.77, 1.60	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				showing signs of acute pyelonephritis				

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Francois P;Bensman A;Beguer P;Artaz MA;Coudeville L;Lebrun T;Scheimberg A; 1997 190	Study Type: RCT Included in Cochrane review (Ref ID 87) Evidence level: 1+	To compare the clinical effectiveness and cost of an oral therapy (cefixime) with the parenteral therapy (ceftriaxone) as a support treatment after an initial intravenous (IV) combination therapy in acute pyelonephritis	Total 147 70 in 4 day IV ceftriaxone 77 in 10 days IV ceftriaxone	Age 0.5 -10 years with acute pyelonephritis UTI and fever >38ºC, pyuria, CRP increased Exclusions: previous acute pyelonephritis, organisms resistant to trial antibiotics. Allergy to cephalosporins, B-lactams, aminoglycosides, known uropathology, need for IV antibiotics based on ultrasound, renal failure, immune deficiency, other inflammation.	Intervention: All received IV ceftriaxone 50 mg/kg/d daily dose and IV netilmicin 6-7.5 mg/kg/d in 3 divided doses for 4 days. Then oral cefixime 4 mg/kg/dose, 2 doses per day for 6 days versus IV ceftriaxone 50 mg/kg/d single daily dose for 6 days Comparison: 4 day IV therapy vs 10 day IV therapy	Follow-up period: 1 month Outcome Measures: Persistant bacteriuria 2 days after end of therapy Recurrent UTI in 20 days after therapy Adverse events	Persistant bacteriuria: 1/63 vs 0/65, RR 3.09 95% 0.13, 74.55 Recurrent UTI: 0/49 vs 2.53, RR 0.22 95% CI 0.01, 4.39 Adverse events:9/67 vs 8/72, RR 1.12 95% CI 0.50, 2.95	Definition of 'success rate' not reported No statistical analyses to take account of potential biases and confounding factors

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Madrigal G;Odio CM;Mohs E;Guevara J;McCracken GH; 1988 191	Study Type: RCT Included in Cochrane review (Ref ID 88) Evidence level: 1+	To evaluate the efficacy of three regimens of TMP/SMX therapy for children with acute uncomplicated UTI.	222 patients enrolled 70 one dose 73 two doses daily for 3 days 79 two doses daily for 7 days	Children aged 3 months to 12 yeaers with suspected or proven acute UTI - diagnostic criteria 100,000 cfu/ml.	Intervention: TMP/SFX One dose Two doses daily for 3 days Two doses daily for 7 days Comparison: Treatment length vs. treatment length	Follow-up period: 28 to 37 days after therapy completion Outcome Measures: Urine steralisation recurrence	There was no difference in bacteriologic cure rates for the single dose regimen (93%) and multidose regimen (96%). The difference in rates of recurrence between single dose (20.5%) and 3 day (5.6%) and 7 day (8%) was statistically significant (p=0.033)	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Noorbakhsh S;Lari AR;Masjedian F;Mostafavi H;Alaghehbandan R; 2004 193	Study Type: RCT Evidence level: 1+	To compare the efficacy of IV aminoglycoside with IV ceftriaxone plus switch therapy to cefixime in children with UTIs	Total 54 30 in ampicillin group 24 in ceftriaxone group	children aged ≤ 10 years with UTI Exclusion criteria: history of serious allergy to study therapy, complete obstruction of the urinary tract, perinephric or intrarenal abscess, any rapidly progressive disease, immune-compromising illness or therapy, the need for concomitant antimicrobials, acute hepatic failure, requirement for peritoneal dialysis or hemodialysis, treatment with a systematic antimicrobial	Intervention: IV amikacin 15 mg/kg daily or gentamicin 3mg/kg daily with ampicillin 100mg/kg daily for 7 to 10 days versus IV ceftriaxone 50mg/kg daily for the first 2 days and then switched to cefixime 8mg/kg daily for 8 days Comparison: threapy vs therapy	Follow-up period: 4-6 weeks post therapy Outcome Measures: Failure of therapy (urine culture of 10,000 colony forming units/ml of any uropathogen present in the admission culture at a concentration of 100,000 colony forming units/ml)	Rate of response (clinically and microbiologically) aminoglycoside 24/30 versus ceftriaxone and switched to cefixine 21/24 (p=0.82)	Poor reporting of results, unsure what outcome 'rate of response' is measuring No power calculation

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				agent for ≥ 24 hours within 72 hours prior to the baseline urine culture, creatinine clearance of < 30 ml/min, aspartate aminotransferase or alanine aminotransferase levels of > 6 times the upper limit of normal, bilirubin or alkaline phosphatase levels of > 3 times the upper limit of normal, absolute neutrophil count of ≤ 1000 per µl, platelet concentration of < 75000 per µl, hematocrit level of < 25%, or coagulation tests of >1.5 times the upper limit of normal.				

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Baker PC;Nelson DS;Schunk JE; 2001[195]	Study Type: RCT Evidence level: 1+	To determine whether the addition of a single dose of ceftriaxone sodium to a 10-day course of trimethoprim and sulfamethoxazole hastens urine sterilization or resolution of clinical symptoms in febrile children with urinary tract infections	69 Total included in analysis (18/87 drop out, 14 due to no growth in their urine culture, 4 did not return for follow up) 34 treated with IM ceftrixone and oral trimethoprim-sulfamethoxazole 35 treated with oral trimethoprim-sulfamethoxazole only	Aged 6 months to 12 years, temperature > 38.0ºC were diagnosed as having a UTI based on presenting history, physical examination and urinalysis findings. Exclusions: known urologic anomaly, were taking antibiotics, had allergies to study medications, or were clinically unstable. Patients subsequently included in the final study sample if they had a positive urine culture (single organism growth > 100000 colony forming units per high-power field from	IM ceftrixone (1 dose of 50 mg/kg) and oral trimethoprim-sulfamethoxazole (twice daily 5 mg/kg per dose for 10 days) versus oral trimethoprim-sulfamethoxazole only (twice daily 5 mg/kg per dose for 10 days)	Follow up: 48 hours Outcome measures: Treatment failure (microbiological and clinical criteria, persistence of bacterial growth in the follow up urine culture after 48h of treatment or subsequent need for hospital admission) Adverse effects	Treatment failure: 4/34 vs 5/35 p > 0.05 Adverse effects: 4/34 vs 3/35 p = 0.96	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				a clean catch urine specimen or greater than 10000 colony forming units per high-power field from a catheterized urine sample).				

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Wallen L;Zeller WP;Goessler M;Connor E;Yogev R; 1983 [194]	Study Type: RCT Included in Keren Meta-Analysis (Ref ID 85) Evidence level: 1+	To compare the effectiveness of a singla intramuscular injection of amikacin sulfate to a 10 day course of sulfisoxazole in treatment of UTI in girls	54 girls 26 received one intramuscular amikacin 28 received 10 oral day sulfisoxazole	Girls aged 1-12 years with suspected UTI and 2 positive cultures. Exclusions: clinical symptoms of pyelonephritis, fever (> 38.3ºC), flank pain, ESR>21mm/hr, antibiotic usage in last week or known urinary tract anomalies	Intervention: Single intramuscular injection of amikacin sulfate compared to 10 day oral sulfisoxazole for the treatment of presumed lower E coli urinary tract infections. Comparison: Treatment vs. treatment	Follow-up period: 3 months. Outcome Measures: Urine steralisation	6/23 receiving IM amikacin and 4/21 receiving oral sulphisoxazole had at least one positive urine culture within 40 days post treatment. Difference no statistically significant (p>0.5)	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Michael M;Hodson EM;Craig JC;Martin S;Moyer VA; 2005 196	Study Type: Systematic review - meta-analysis Evidence level: 1++	To assess the benefits and harms of short-course compared to conventional therapy for acute UTI in children.	910 children entered Outcomes evaluated in 652. 168 loss to follow up 99 excluded because no long-duration comparison group	Children 3 months - 18 years with culture proven UTI. Excluded children with neurogenic bladders and known urinary tract abnormalities. RCTs did not specify whether patients were symptomatic or asymptomatic	Intervention: Antibiotic treatment - RCTs only Comparison: Short v standard duration oral antibiotic therapy	Follow-up period: 33 days - 12 months Outcome Measures: Primary Outcomes - Persisting clinical symptoms at the end of treatment - Significant bacteriuria (>10,000 organisms/ml) at completion of Rx - Recurrent UTI after Rx (one month or more) Secondary Outcomes - Compliance with medication - Development of resistant organisms - Cost - Side effects	Significant bacteriuria 8 data sets (RR 1.06, 95%CI 0.64 to 1.76) 0-10 days after completing treatment. Sulphonamides alone or in combination with trimethoprim and other antibiotics - sulphonamide group 4 studies (RR8.80, 95%CI 0.45 to 1.41) - other antibiotics 4 studies (RR1.72, 95%CI 0.64 to 3.80) Abnormal IVP or MCUG (RR0.99, 95%CI 0.70 to 1.29) But heterogeneity Recurrent UTI 1-15 months FU 10 data sets (RR 0.95, 95%CI 0.70 to 1.29) Recurrent + abnormality (RR0.24 95%CI 0.03 to 1.67) Compliance 3 studies reported satisfactory compliance Resistance urinary pathogens resistant or persistent bacteriuria one study (RR 0.57 95%CI 0.12 to 1.29) Recurrent UTI Three studies (RR 0.39 95%CI 0.12 to 1.29) RRR for resistant organisms 43% for	Enrolled both symptomatic and asymptomatic patients Studies included were generally small and included children from a wide age range. Review looks fine but individual RCTs are a bit dodgy.

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
							bacteriuria at end of Rx and 61% recurrent.	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Chong CY;Tan AS;Ng W;Tan-Kendrick A;Balakrishnan A;Chao SM; 2003 197	Study Type: RCT Included in Cochrane review (Ref ID 87) Evidence level: 1+	To examine the safety and efficacy of once daily gentamicin treatment ccompared with conventional 8 hourly dosing.	Total 172 (analysed of 210 recruited) 84 in once daily group 88 in three times daily group	Age 1 month to 13 years, (mean age 0.92 ± 1.30 years) with presumed UTI (fever >38ºC with pyuria, >200 white blood cells/ml or foul smelling urine, dysuria, frequency of micturition or loin pain). UTI confirmed on 2 clean catch urines (single organism > 100,000ml) or 1 catheter specimen (single organism >1000/ml) Exclusions: < 1 month of age (or if born prematurely with a corrected age of <24 weeks) history of previous allergy to aminoglycosides,	Intervention: IV gentamicin 5 mg/kg/d given over 1 hour once a day versus IV gentamicin 6 mg/kg/d given over 20-30 minutes three times a day Comparison: once daily treatment vs three times daily treatment	Follow-up period: 3 months Outcome Measures: Persistent bacteriuria (negative urine culture at end of gentamicin treatment) Time to defervescence Nephrotoxicity (increase in creatinine by 50% or more) Renal scar on DMSA scan at 3 months	Persistent bacteriuria: 2/84 vs 2/88, RR 1.05, 95% CI 0.15, 7.27 Time to defervescence: 47.4 ± 34.6 vs 45.0 ± 34.4 RR 2.40, 95% CI -7.90, 12.70 Nephrotoxicity: 1/79 vs 2/80 RR 0.51, 95% CI 0.05, 5.47 Renal scar on DMSA scan at 3 months: 18/75 vs 23/71 RR 0.66 95% CI 0.32, 1.36	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				renal impairment with abnormal serum creatinine at baseline or known renal impairment, previous nephrotoxic drugs in the last month, concurrent nephrotoxic drugs, known obstructive uropathy, known hearing impairment or abnormal baseline otoacouistic emission.				

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Carapetis JR;Jaquiery AL;Buttery JP;Starr M;Cranswick NE;Kohn S;Hogg GG;Woods S;Grimwood K; 2001 198	Study Type: RCT Included in Cochrane review (Ref ID 87) Evidence level: 1+	To determing the safety and efficacy of once daily gentamicin dosing in children with severe UTI	184 children (179 analysed) 90 in once daily group 89 in three times daily group	Age 1 month to 12 years Ill, vomiting and unable to take oral medication reliably. UTI diagnosed by identifying uropathogens in suprapubic aspirate specimens or a pure growth of ≥100000 bacteria/ml in catheter or midstream urine specimens. Exclusions: aminoglycoside hypersensitivity, known gentamicin-resistant organisms, renal impairment, hearing loss, vestibular disease, neutropenia or immunodeficiency	Intervention: once daily IV gentamicin versus three times daily IV gentamicin In both groups gentamicin given as 30 min infusion 7.5 mg/kg for < 5 year olds, 6.0 mg/kg for 5-10 year olds, 4.5 mg/kg for >10 year olds, treatment length varied Comparison: once daily treatment vs three times daily treatment	Follow-up period: Dependent on last day of treatment. Treatment continued until particpants were afebrile for 24h, then oral therapy determined by the antibiotic susceptibility was started Outcome Measures: Cure (resolution of the presenting symptoms and signs without use of other antibiotics Partial resolution Failure (persistence of the original symptoms and signs) Time to fever resolution	Cure 86/90 vs 87/89, RR 0.98, 95% CI 0.93, 1.03 Partial resolution 4/90 vs 2/89 Failure 0/90 vs 0/89 Time to fever resolution: 27 (13.5-47.5) vs 31.0 (9.8-48)h (p = 0.61)	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Vigano A;Principi N;Brivio L;Tommasi P;Stasi P;Villa AD; 1992 Jul 199	Study Type: RCT Included in Cochrane review (Ref ID 87) Evidence level: 1+	To evaluate the efficacy of netilmicin.	150 in total (6 droped out) 74 treated with IM netilmicin 5 mg/kg once daily. 70 were treated with IM netilmicin 2 mg/kg three times a day.	Age 1 month to 12 years with UTI (two urine samples collected by the clean catch method or bladder catheterization containing ≥100,000 colony forming units of gram negative bacteria per ml) signs and symptoms of pyelonephritis (body temperature, ≥ 38.5ºC, erythrocyte sedimentation rate, > 25 mm/l h, C-reactive protein, > 20 µg/ml) Exclusions: hypersensitivity to aminoglycosides, serum creatinine values abnormal for age,	Intervention: IM netilmicin 5mg/kg of body weight once daily versus IM netilmicin 2 mg/kg three times a day Comparison: once daily treatment vs three times a day treatment	Follow-up period: 6 weeks Outcome Measures: Persistant bacteriuria at 7 days and recurrent UTI by 30 days after end of therapy Adverse effects	Persistant bacteriuria at 7 days: 1/74 vs 0/70 Recurrent UTI by 30 days after end of therapy: 5/74 vs 4/70, RR 1.18 95% CI 0.33, 4.23 Adverse effects:hearing impairment 2/20 vs 0/12 increasein serum creatinine2/74 vs 2/70	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				presence of ileostomies, ureterostomies or neurogenic bladder and a history of signs of deafness				

1

2

Cranberry

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Jepson RG;Mihaljevic L;Craig J; 2005 [204]	Study Type: Systematic review - meta-analysis Evidence level: 1++	To assess the effectiveness of cranberries for the treatment of urinary tract infections.	No trials found	Searched for studies	Intervention: Effectiveness of cranberry juice and cranberry products for the treatment of UTI Comparison: No trials found	Follow-up period: Outcome Measures: Outcomes searched were number of symptomatic and asymptomatic UTIs at the end of treatment period.	No trials assessing the treatment of UTIs with cranberry juice were found. Two uncontrolled trials have shown a beneficial effect but no conclusions can be drawn from such studies.	

1 Antibiotic treatment for asymptomatic bacteriuria

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Savage DC;Howie G;Adler K;Wilson MI; 1975 200	Study Type: RCT Evidence level: 1+	To decide whether prescriptive screening of school age girls is necessary by investigating the effect of antibiotic therapy.	63 girls, 34 in the control group and 29 in the treated group.	Girls aged 5 to 7 years 10 months found to have covert bacteriuria during a screening program of 5 year old girls entering school in 1969 and 1970 in Dundee. Girls were also included who had been detected in 1968 and re-screened in 1969 and 1970. Girls with history of urinary tract infection were excluded.	Intervention: Children with normal IVP and MCUG received 3 months prophylaxis initially and after their first relapse. Later relapses received 6 months prophylaxis. Children with evidence of pyelonephritis and/or VUR received 6 months prophylaxis, and following a relapse, 6-12 months was given. Prophylactic antibiotics were ampicillin, nitrofurantoin or co-trimoxazole. Comparison: Treatment vs. no treatment	Follow-up period: 3 years. Mean period of follow up 44 months (28 to 68 months) Outcome Measures: Persistent infection Recurrent infection Radiological abnormalities Renal growth	PERSISTENT OR RECURRENT INFECTION Treatment group vs. control group Persistent or recurrent infection Within 6 months: 7/29 (24%) 22/32 (69%) ($p<0.01$) Within 12 months: 14/29 (48%) vs. 24/32 (75%) Within 2 years: 20/27 (74%) vs. 27/32 (84%) Infected urine in 3rd year: 11/27 (41%) vs. 19/30 (63%) 4th year: 12/26 (46%) vs. 16/27 (59%) Number of recurrences during years 3 and 4 7/26 (27%) vs. 5/27 (19%) Number of recurrences since diagnosis 6/29 (21%) vs. 3/32 (9%) Treatment group (normal radiology, abnormal radiology) vs. control group (normal radiology vs, abnormal radiology) Persistent or recurrent infection Within 6 months: (16/24 (67%), 6/8 (75%)) vs. (4/18 (22%), 3/11 (27%)) ($p<0.05$) Within 12 months: (18/24 (75%), 6/8 (75%)) vs. (11/18 (61%), 3/11 (27%))	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
							Within 2 years: (20/24 (83%), 7/8 (88%)) vs. (12/18 (67%), 8/9 (89%)) Infected urine in 3rd year: (13/22 (59%), 6/8 (75%)) vs. (8/18 (44%), 3/9 (33%)) 4th year: (11/19 (58%), 5/8 (63%)) vs. (7/18 (39%), 5/8 (63%)) Number of recurrences during years 3 and 4 (4/19 (21%), 1/8 (13%)) vs. (5/18 (28%), 2/8 (25%)) Number of recurrences since diagnosis (3/24 (13%), 0/8 (0%)) vs. (5/18 (28%), 1/11 (9%)) RADIOLOGY 20/29 children in the treatment group were available for radiological investigation 2 years after initial diagnosis, while 30/34 children in the control group were available. Treatment group Normal renal tract (n=17). 16 no change, 0 improved, 1 worse. Pyelonephritis and/or reflux (n=10). 6 no change, 2 improved, 2 worse. Control group Normal renal tract (n=22). 20, no change, 0 improved, 2 worse	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
							Pyelonephritis and/or VUR (n=8). 4 no change, 1 improved, 3 worse. RENAL GROWTH Initial renal length in cm (mean ± sd) Treated, normal radiology (n=26 kidneys) 9.13 ± 0.69 Controls, normal radiology (n=49 kidneys) 9.15 ± 0.81 Treated, abnormal radiology (10 kidneys) 8.9 ± 1.1 Controls, abnormal radiology (11 kidneys) 8.7 ± 1.1 Renal growth in 32 years in cm (mean ± sd) Treated, normal radiology (n=20 kidneys) 0.95 ± 0.58 Controls, normal radiology (n=37 kidneys) 0.67 ± 0.33 Treated, abnormal radiology (7 kidneys) 0.43 ± 0.31 Controls, abnormal radiology (9 kidneys) 0.44 ± 0.41	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Selkon JB;Roxby CM;Sprott MS; 1981 201	Study Type: RCT Evidence level: 1-	To investigate whetner screening programmes can be recommended by showing whether tretment of asymptomatic bacteriuria and progressive scarring can be prevented by prophylaxis.	252 girls, 41 found to have renal involvement at the initial assessment were given prophylaxis, while 211 girls were randomised to receive prophylaxis (n=105) or no treatment (n=106).	Girls aged 4 to 18 years found to have covert bacteriuria during a school screening program between 1968 and 1972 in Newcastle. Bacterial count of 10^5 organisms/ml in at least 2 of the 3 specimens was considered to have significant bacteriuria and was referred to hospital. Girls with history of urinary tract infection were excluded.	Intervention: Initial examination included 6 mid-stream urine samples collected at weekly intervals, IVU and MCUG. Girls found to have initial renal involvement were prescribed prophylaxis for 2 years and each was reviewed on a cse-by-case basis following the two years. Girls in the prophylaxis group were given a 2 year course of either co-trimoxazole, nalidixic acid, ampicillin or nitrofurantoin and treatment was stopped after 2 years if it had been effective in the previous 6 months. If during follow up children randomised to the no treatment group developed symptoms suggesting a UTI and had a positive	Follow-up period: All children were seen at 3 and 6 months after the first investigation and then at intervals of 6 months. At the 2 year and 5 year visits, IVU was repeated. MCUG was repeated at the clinicians discretion. Outcome Measures: Natural resolution of bacteriuria Symptomatic UTI Renal growth	No treatment Number becoming abacteriuric at each visit (cumulative total) 1st visit – 5 (5) 3 months – 7 (12) 6 months – 3 (15) 1 year – 7 (22) 2 years – 4 (26) 3 years – 7 (33) 4 years – 9 (42) 5 years – 6 (48) Among the 52 remaining girls, 23 had been given antibiotics at some time during the follow up period either for symptomatic UTI, or for other infections. There were no significant differences in the proportion of girls who became abacteriuric by age. SYMPTOMATIC DISEASE No treatment Acute pyelonephritis = 5 Symptoms suggesting cystitis = 4 A further 9 girls were prescribed antibiotics for pyuria, frequency, haematuria, enuresis or poor kidney growth over the 5 year period. An additional 5 were prescribed antibiotics for other infections. Prophylaxis	Not all girls recruited were randomised. This will over-estimate the treatment effect.

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
					cultures, 10 day antibiotic treatment was given. Comparison: Treatment vs. no treatment		Acute pyelonephritis = 3 Symptoms suggesting cystitis = 7 A further 5 were prescribed antibiotics for other infections. RADIOLOGY Radiology measurements were available for analysis in 91 girls in the prophylaxis group and for 92 in the no treatment group. Follow up data was available from 173 children at 2 years and for 112 at 5 years. Regression analysis showed no differences in renal growth over 5 years between the groups. In children with initially Normal renal tract (n=22). 20, no change, 0 improved, 2 worse Pyelonephritis and/or VUR (n=8). 4 no change, 1 improved, 3 worse.	

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Lindberg U;Claesson I;Hanson LA; 1978 202	Study Type: RCT Evidence level: 1-	To describe the clinical course of treated or untreated asymptomatic bacteriuria over three years in school aged girls.	116 girls with asymptomatic bacteriuria identified and after exclusion od those with scarring and/or reflux, and then those in whom bacteriuria was eliminated 61 girls were randomised, 31 in the control group and 30 in the treated group.	Girls aged 7 to 15 years found to have asymptomatic bacteriuria during a screening program. Bacterial count of 10^5 organisms/ml was considered to be significant bacteriuria.	Intervention: IVP and MCUG after three years of follow-up. Antibiotic therapy for symptomatic cystitis was 10 day nitrofurantoin and for pyelonephritis sulphafurazole. Prophylaxis was nitrofurantoin. Comparison: Treatment vs. no treatment	Follow-up period: Outcome Measures: Bacteriuria on follow up Symptomatic UTI	27/30 children in the treatment group were followed up for three years. 9/27 (33%) were given long-term prophylaxis because of repeated recurrences; 6/9 continued to have recurrences after 3 years prophylaxis. 13/27 required antibiotic treatment (short-course) for an episode of bacteriuria, and an additional 5/27 required two short courses of treatment, however there were no further recurrences in either group. 30/31 children in the untreated group were followed for 3 years. 9/31 (30%) became spontaneously abacteriuric and none had recurrences. 5/31 (17%) became abacteriuric after penicillin for respiratory infection. 1/30 (3%) had symptomatic pyelonephritis and 1/30 (3%) had dysuria during an episode of measles. 14/30 (47%) remained bacteriuric after three years. Growth of kidneys in these children was normal, there were no signs of scarring. One child developed grade I reflux. There were no significant differences in the number of bacteriuric children in the treatment group (6/27) compared to the untreated group (14/30) at the end of the observation period.	Only half of the original number of girls recruited were randomised. This will over-estimate the treatment effect. Allocation concealment not reported Blinding not reported

Bibliographic Information	Study Type & Evidence Level	Study Aims	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
1978 Apr 29 [203]	Study Type: RCT Evidence level: 1-	To determine the sequeale of covert bacteriuria in girls of school age and whether treatment could prevent any or all of the effects.	208 girls (110 girls treated 98 girls not treated)	Girls identified as having cover bacteriuria for screening study [238] Bacteriuria defined as <10^5cfu/ml in at least 2 consecutive mid-stream samples.	Intervention: Treatment with antibacterial therapy for bacteriuria (usually given co-trimoxazole but also ampicillin, nitrofurantoin, nalidixic acid and pivmecillinam, initally 7 or 14 day course were given but longer courses at discresion of Dr) Controls received no treatment During the study period (date of first x-ray till the date of the second, mid-stream urine samples were collected monthly in one health distric (Oxford) and every two months in the other (Cardiff). Comparison: treatment versus control	Follow-up period: from date of first x ray to second four years (± 0.3 years) later. Outcome Measures: time free from infection emergence of symptoms clearence of VUR kidney growth progression of kidney scars	Bacteriuria at end of study: 17/110 (15%) in treatment girls and 44/98 (45%) in girls with no treatment (chi2=20, p < 0.001) 28/98 (29%) in the treatment group were scarred at the first x-ray 12/110 (15%) in the treatment group were scarred at the first x-ray No new scars were seen in girls who had normal kidneys at the initial x-ray examination Of the girls with scars at the initial x-ray new and/or deepening scars were found in 12/44 (27%). 6/28 (21%) in the girls who received treatment and 6/16 (38%) in the girls who received no treatment.	Allocation concealment not reported. Blinding not reported 7 girls excluded - reason for exclusion unknown. Loss to follow-up was 13% in the treated group and 19% in the control group. This is a 16% loss overall. No explanation of whether those lost were similar to the girls followed-up. Did not use intention to treat analysis.

1

1 Factors predicting recurrence

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
Shaikh N;Hoberman A;Wise B;Kurs-Lasky M;Kearney D;Naylor S;Haralam MA;Colborn DK;Docimo SG; 2003 [205]	Study Type: Cohort Evidence level: 2+	To evaluate the relationship between early UTI, VUR and dysfunctional elimination syndrome.	UTI cohort = 123 (115 girls and 8 boys) Comparison cohort = 125 (120 girls and 5 boys)	UTI Cohort: Children aged 4.3 to 10.6 years previously enrolled in a prospective multi-centre UTI treatment trial conducted between 1992 and 1997 who received a diagnosis of febrile UTI before 2 years old. Non-UTI cohort: Children aged 4.3 to 10.6 years identified retrospectively (and randomly) who as part of an evaluation for fever had a negative urinalysis and culture performed during	547 questionnaires mailed to eligible subjects (168 in the UTI cohort and 406 in the comparison cohort). 248 completed questionnaires were returned. Questionnaire return rates in the UTI cohort were 73% and in the comparison cohort 31%.	Dysfunctional elimination symptoms were assessed with the dysfunctional voiding scoring system (validated).	The groups were similar with respect to demographic and clinical characteristics. The prevalence of dysfunctional elimination syndrome did not differ between children with UTI and children without (22% vs. 21%, p=0.82). In children with UTI, the prevalence of dysfunctional elimination syndrome did not differ in children with or without VUR (18% vs. 25%, p=0.52). Further analysis using different cut-off values did not yield different results. 31 children had recurrent UTI. Of these 13 (43%) had encopresis (OR 2.5, 95%CI 1.1 to 5.4, p=0.03), 11 (36%) had dysfunctional elimination syndrome (OR 2.2, 95%CI 0.99 to 5, p=0.05) and 17 (55%) had VUR (OR 2.2, 95%CI 0.9 to 5, p=0.07). The only variable that remained significant with recurrent UTI was encopresis (p=0.03).	Inadequate statistical analysis - Included one non-significant variable, and one borderline significant variable in a multivariable model of only 3 variables. Including non-significant variables will make the model more 'fuzzy' although it is unlikely to change the conclusions.

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
				the same period (1992 to 1997). Negative urinalysis: <10 WBC/mm^3 on a haemocytometer in an uncentrifuged specimen. Positive urine culture: At least 10^4cfu/ml on catheter sample or 10^5cfu/ml on a clean voided specimen. Recurrent UTI: More than one confirmed UTI.				

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
Panaretto KS;Craig JC;Knight JF;Howman-Giles R;Sureshkumar P;Roy LP; 1999 [61]	Study Type: Cohort Evidence level: 2++	Evaluated the risk factors that predispose to recurrent UTI in children and the role of recurrent UTI in renal scarring.	290 children with first UTI	Children (n=133 female, n=157 male), aged under 5 years, presenting at a children's hospital with first time UTI between March 1993 and December 1994 Exclusions: Known predisposing renal, neurological or skeletal causes. UTI defined as: for SPA or catheter, >10^6 cfu/l (n=164); for clean catch or midstream, >10^7 cfu/l (n=107); for bag urine, 10^8 cfu/L and white cell count >10^8/L Recurrent Infection: Recorded as per	Characteristics of recurrent UTI examined to identify groups at increased risk for recurrent UTI MCUG (at median 29 days, range 5 to 127 days following initial UTI) DMSA (at 7 days, range 0 to 34 days)	Rate of FU No. with VUR at entry No. with fever with UTI at entry No. with recurrence (confirmed with microbiology) Odds ratios (95% CI) Follow-up period: 1 year.	At the initial UTI, VUR was found in 83/290 (29%) of children and renal parenchymal defects in 113/290 (39%). Fever was present in 233/290 (80%) of children at index UTI. At 1 year, 261 (90%) children still in study, 133 girls and 157 boys with median age 1.2 years (range 10 days to 5 years) and at one year follow up was 2.3 years (range 1 to 6 years). 46 recurrent UTI episodes in 34 children - 20 had one recurrence - 14 had two recurrences Gender (OR 1.5, 95%CI 1 to 2.2, p=0.08) Fever (OR 1.2, 95%CI 0.7 to 2, p=0.59) Age <6 months (OR 2.9, 1.4 to 6.2, p<0.01) VUR (OR 1.3 95%CI 0.6 to 2.5, p=0.50) Dilating VUR (OR 3.6, 95%CI 1.5 to 8.3, p<0.001) Intrarenal VUR (OR 1.3, 95%CI 0.6 to 3.2, p=0.54) Bilateral VUR (OR 1.2, 95%CI 0.6 to 2.3, p=0.6) Abnormal entry DMSA (OR 1.5 95%CI 0.7 to 3.5, p=0.32) VUR was present in 14/34 (41%) with recurrent infection and 65/256 (27%) without recurrent infection. Presence of reflux was not associated with recurrent infection (p<0.05) but the grade of reflux (X2=12.1, p<0.01), bilateral reflux (x2=6.1, p<0.05) and intrarenal reflux (x2=5.2, p<0.05) were	Study may be insufficiently powered to detect differences between exposed and unexposed groups. Univariate analysis not reported.

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
				parental report and documented with confirmatory microbiological analysis.			significantly associated with recurrence. High grade reflux (grades 3 to 5) was an independent predictor of recurrence (OR 3.6, 95%CI 1.5 to 8.3, p<0.001) Renal parenchymal defects Repeat DMSA was performed in 173 children at 1 year. Recurrent UTI was significantly associated with renal parenchymal defects seen on first UTI (X2=4.6, p<0.05), grade of DMSA abnormality on entry (X2=12.3, p<0.01), DMSA abnormalities at one year (X2=11.5, p<0.001) and renal parenchymal defects at one year (X2=10.1, p<0.001)	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
Stauffer CM;van der WB;Donadini R;Ramelli GP;Marchand S;Bianchetti MG; 2004 Apr [206]	Study Type: Case control Evidence level: 2+	To evaluate the role of family history, infrequent voiding, poor fluid intake, functional stool retention and inadequate anogenital hygiene or toilet habits in girls with recurrent UTIs.	90 cases 45 controls	Cases: Girls aged 3.9 to 16 years (median 8.4 years) referred to a nephrology clinic for evaluation of three or more symptomatic UTIs. Controls: Girls aged 4.0 to 14 years (median 7.3 years) none of whom had history of UTI. Controls had: - History of idiopathic childhood nephrotic syndrome cured for 2 years or more (9) - Allergic rhinitis (19) - Treated celiac disease (12) - Tension-type headache (5) Exclusions: first	Written questionnaire evaluated family history, urinary, bowel and toilet habits, and anogenital hygiene by closed questions. The volume of any intake or urination was recorded for three days by a voiding-drinking diary. Non-invasive urodynamic assessment was completed. The diagnosis of dysfunctional voiding was made in girls with an interrupted urinary stream and unsustained relaxation of the pelvic floor muscles during micturation.	Volume of any intake or urination (by graduated measuring cup) Infrequent voiding (include at least 2 of the following) - habit of passing urine 3 or less times daily - voiding postponement - increased daytime bladder capacity - daytime urinary incontinence Functional stool retention (at least 3 of the following) - 72-hour or more interval between bowel movements - habit of passing small hard stools - history of painful defecation	90 cases 60 had a history of lower UTI 30 had history of mixed UTI, upper in 16 and both upper and lower in 14. Family history of UTI (42% of cases v 11% of controls, p<0.001), Behavioural abnormalities (81% v 56%, p<0.01) Infrequent voiding (54% v 24%, p<0.001) Poor fluid intake (53% v 16%, p<0.001) Functional stool retention (30% v 13%, p<0.05) There were no significant differences between cases and controls for anogenital hygiene or toilet habits.	Not clear whether the same exclusion criteria was applied to both cases and controls Participation rates unclear Control selection unclear - don't know where they were selected from or why. No definition of bacteriuria or 'suggestive symptoms'

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
				infection under 36 months, asymptomatic infection, adolescents with a history of sexual activity, history or findings suggestive of sexual abuse, known urinary tract malformations, neuropathic bladder, moderate to severe mental retardation, disorders of posture or movement, overt encopresis.		- stool retention on abdominal examination after defecation. Poor fluid intake (from beverage and plain water) Daily fluid intake of less than 600ml/m^2 body surface area or less Inadequate anogenital hygiene or toilet habits (at least 3 of the followint) - underpants frequently contaminated with fecal material at the end of the day - passing toilet paper back to front or using the same piece of paper 2 or more times - use of tight fitting clothes		

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
						- toilet trained child aged 5 years or less - small children using regular toilets (rather than a potty chair)		

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
Biyikli NK;Alpay H;Guran T; 2005 Oct [213]	Study Type: Case series. Evidence Level: 3	To survey the incidence of idiopathic hypercalciuria in children with recurrent UTI.	75 children (62 girls, 13 boys)	Children aged 8 years (±2.7 years) with recurrent UTI. Recurrent UTI: two or more episodes of UTI separated for a period by sterile urine culture and symptom-free interval UTI: More than 10^5cfu/ml in mid-stream clean catch urine Hypercalciuria: the average urinary calcuim/creatinine ratio (mg/mg) equal or greater than 0.24 measured in at least 3 random morning urine samples in order to minimize the daily variation, or 24-hour urinary	Ultrasonography for urinary tract abnormalities DMSA for evaluating scar formation	Age at presentation Gender Presenting complaints Family history of urolithiasis Random urinary calcium/creatinine value (measured three times mg/dl) 24-hour calcium excretion (measured by cresolphthalein complexone spectrophotometric method mg/dl) Serum calcium Phosphorus, Electrolytes Blood gas Blood urea nitrogen and creatinine levels	Hypercalciuria was found in 32 children (43%) of whom 23 (72%) were girls and 9 (28%) were boys. (hypercalciuric children vs. normocalciuric children) Mean age (years) 7.2 ± 2.1 vs. 8.7 ± 2.9, p=0.013 Mean calcium/creatinine ratio 0.50 ± 0.21 vs. 0.10 ± 0.04, p=0.01 Voiding dysfunction 20 (63%) vs. 25 (58%) p=0.663 Pain 16 (50%) vs. 29 (67%) p=0.171 Haematuria 11 (35%) vs. 14 (33%) p=0.683 Urolithiasis 2 vs. 0 p=0.064 Family history of urolithiasis 19 (59%) vs. 20 (47%) p=0.414 Predisposing urinary tract abnormality 12 (38%) vs. 8 (19%) p=0.067	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
				calcium excretion greater than 4mg/kg per day in patients who were found to be hypercalciuric in random urinary excretion of calcium/creatinine ratio (mg/mg).				

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
Bratslavsky G;Feustel PJ;Aslan AR;Kogan BA; 2004 Oct [208]	Study Type: Case-series. Evidence Level: 3	To evaluate the rate of and potential risk factors for recurrent UTI in children with UTI and no abnormality on radiographic evaluation.	264 infants of whom 119 met the inclusion criteria. Follow up data was available for 84 (52 girls and 32 boys)	Children younger than 6 months who had a normal ultrasound and VCUG. Mean age at follow-up 4.8 years (range 2.3 to 7.2 years)	Questionnaire administered over the telephone	UTIs (febrile or non-febrile) Duration of breast feeding Type of formula Family history of UTI Neurological problems History of constipation or recurrent fevers Socio-economic status Mean follow-up period 4.4 years (range 1.9 to 7.0 years)	16/84 (19%) had at least one febrile UTI after the negative radiographic evaluation. Number with recurrent UTI vs. Number with no recurrent UTI, p-value Breast-feeding (less than 4 months) 13 (81%) vs 39 (57%) p=0.077 Siblings younger than 14 years 12 (75%) vs. 60 (88%) p=0.680 Family history of UTI 9 (56%) vs 29 (43%) p=0.325 Potty training (less than 2 years) 6 (38%) vs 18 (26%) p=0.640 Neurological problems 0 (0) vs. 3 (4%) p=0.687 Undiagnosed fevers 5 (31%) vs 9 (13%) p=0.082 Constipation history 2 (13%) vs. 11 (16%) p=0.714	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
							Residence (live in private house) 12 (75%) vs. 55 (81%) p=0.598 Income less than $50,000 8/13 (62%) vs. 31/57 (54%) p=0.344 Circumcision 2/3 (67%) vs. 17/28 (61%) p=0.841	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
Bakker E;Van Gool J;Van Sprundel M;Van Der Auwera JC;Wyndaele J; 2004 [209]	Study Type: Cross-sectional Evidence level: 3	To investigate the possible relationship between recurrent UTI and methods of potty training by comparing the methods used in children with and without recurrent UTI.	4332 questionnaires completed (2215 boys and 2117 girls)	Children completing the last two years of primary school. Mean age of responders was 11.5 ± 0.56 years. Questionnaire given to 5646 and completed by 4332	4332 questionnaires were completed (response rate 77%) and split into three groups 382 (9%) children with a single UTI (99 boys and 283 girls) 132 (3%) children with recurrent UTI (31 boys and 101 girls) 3818 (88%) children who had no history of UTI (2085 boys and 1733 girls).	No. of UTIs Age at UTI Wetting and soiling Potty training	No differences were observed between the three groups with respect to age. Any UTI Girls vs. boys 18.3% vs. 5.4% (p<0.001) Recurrent UTI group (n=132) 17/31 (51%) boys vs. 21/101 (21%) girls (p<0.001) contracted their first UTI under the age of 2.5 years. Daytime wetting (12%) vs. no daytime wetting (2%) (p<0.001) 9/31 (29%) boys with daytime wetting vs. 31/101 (31%) girls. Faecal soiling Recurrent UTI (9.1%) vs. no recurrent UTI (2.5%) Nocturia at least once a week Recurrent UTI 14/132 (10%) vs. No history of UTI 130/3818 (3%) P<0.001 Potty training started before 18 months old Recurrent UTI 21% vs. No history of UTI 31% P<0.05	History of UTI not confirmed. This is a major limitation of the study and results should be interpreted appropriately cautiously. P-values not accompanied by actual numbers on 1 occasion – Recurrent UTI significantly higher in those with voiding frequency of 10 times or more per day (p<0.02). These have been omitted from the results because they cannot be checked or re-calculated.

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
							Reaction of parents when an attempt to void was unsuccessful Kept child on potty until void was obtained Recurrent UTI 9/79 (11%) vs. No history of UTI 89/2567 (3%) P<0.005 Push/strain Recurrent UTI 17 (13%) vs. No history of UTI 263 (7%) P<0.001 Turned on the tap Recurrent UTI 42 (32%) vs. No history of UTI 826 (22%) P<0.001	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
Mazzola BL;von Vigier RO;Marchand S;Tonz M;Bianchetti MG; 2003 Jan [210]	Study Type: Case-series. Evidence Level: 3	To evaluate the role of family history, infrequent voiding, poor fluid intake, functional stool retention and inadequate anogenital hygiene or toilet habits in girls with recurrent UTIs.	141 girls	Girls aged 3.9 to 18 years (median 6.5 years) referred to a nephrology clinic for evaluation of three or more symptomatic UTIs. None of the girls had a recent UTI (6 weeks or less). 81 were referred by GPs and 60 referred by paediatricians. Exclusions: first infection under 36 months, asymptomatic infection, adolescents with a history of sexual activity, history or findings suggestive of sexual abuse, known urinary tract malformations,	Complete history, bowel and bladder questionnaire, physical and neurological examination and urinalysis. A bladder scan measured post-micturation volume The volume of any intake or urination was recorded for three days by a voiding-drinking diary.	Lower tract infection: history of alguria, incontinence, urgency, frequency or suprapubic pain. Upper tract infection: Additional history of chills, fever (rectal body temperature 38.5°C or more) and abdominal or back pain. Volume of any intake or urination (by graduated measuring cup) Infrequent voiding (include at least 2 of the following) - habit of passing urine 3 or less times daily - voiding postponement	124/141 (aged 7.8 years range 5.7-10 years) had history of lower tract infection. 17/124 (9.1 years, range 5.7-11) had mixed UTI, upper in 5 and both upper and lower in 12. According to the working definitions no behavioural or functional abnormalities were found in 20/141 (14%) of girls with recurrent UTI. 212 abnormalities were found in 121 girls (aged 8.1 years, range 6-10 years). Two, three or four concomitant abnormalities were found in 66 patients. Girls without abnormalities were significantly younger (5.1 years, range 3.3-7.9 vs. 8.1 years, range 6-10, $p<0.05$). Girls with dysfunctional voiding (n=25) were significantly older than other girls with abnormalities (n=96) (10.1 years, range 7.6-11, $p<0.02$ – mean and range for remaining 96 girls not reported). Infrequent voiding 63/141 (45%) Poor fluid intake 60/141 (43%) Functional stool retention 30/141 (21%) Inadequate genital hygiene 27/141 (19%) Dysfunctional voiding 25/141 (18%) Bladder over-activity 7/141 (5%) In micturating cystourethrogram performed in 61 patients. Of the 32 with voiding	Very similar study to study carried out in 2001-2003, but covered 1996-1999. Same inclusion/exclusion criteria and outcome measures. No definition of bacteriuria

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
				neuropathic bladder, moderate to severe mental retardation, disorders of posture or movement, overt encopresis.		- increased daytime bladder capacity - daytime urinary incontinence Presumed dysfunctional voiding (including at least 5 of the following) - habit of passing urine 3 or less times daily - voiding postponement - increased daytime bladder capacity - daytime urinary incontinence - diminished sensation of bladder fullness - staccato or fractionated voiding - incomplete bladder emptying Bladder overactivity (at	dysfunction, 13 (41%) were found to have vesicoureteral reflux. Refux was unilateral in 12 (grade I in 4, grade II in 6 and grade III in 2 patients) and bilateral in one case (grade III). Among the 29 remaining patients vesicoureteral reflux was found in 10 (34%). Unilateral in 7 (grade I in 2, grade II in 3 and grade III in 2 patients) and bilateral in 3 patients (one patient each in grade I, II and III)	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
						least 3 of the following) - habit of passing urine 7 or more times daily - frequent attacks of imperative urge to void - daytime urge incontinence - hold or squatting maneuvers - reduced daytime bladder capacity Functional stool retention (at least 3 of the following) - 72-hour or more interval between bowel movements - habit of passing small hard stools - history of painful defecation - stool retention on abdominal		

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
						examination after defecation. Poor fluid intake (from beverage and plain water) Daily fluid intake of less than 600ml/m^2 body surface area or less Inadequate genital hygiene or toilet habits (at least 3 of the following) - underpants frequently contaminated with fecal material at the end of the day - passing toilet paper back to front or using the same piece of paper 2 or more times - use of tight fitting clothes - toilet trained child aged 5		

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
						years or less - small children using regular toilets (rather than a potty chair)		

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
Ece A;Tekes S;Gurkan F;Bilici M;Budak T; 2005 Aug [211]	Study Type: Case-control Evidence level: 3	To investigate whether the angiotensin converting enzyme (ACE) and angiotensin II type 1 receptor gene polymorphisms were associated with the renal scar formation secondary to recurrent UTI in children without uropathy. Only baseline data from this study was used.	97 children (81 girls and 16 boys)	97 children with recurrent UTI (16 males and 81 females) aged 6.34 years (± 3.16 years). Exclusions: Underlying primary VUR, neurogenic bladder, bladder dysfunction, lower urinary tract obstruction, renal hypoplasia, ectopic kidney. Definition of UTI: Fever, flank pain, increased ESR, positive CRP, positive urine culture, positive LE or nitrite dipstick. Recurrence at least two attacks of UTI in a patient – cystitis was not regarded as a recurrent UTI.		Age at first UTI Renal scarring (on DMSA performed following 3 month period free from UTI) Number of recurrences Micro-organism isolated	Children with renal scarring vs. children with no renal scarring, p-value Recurrent UTI (6.90 ± 2.45 UTI episodes vs. 3.35 ± 1.48 UTI episodes, p<0.001) Age at initial UTI (2.61 ± 1.52 years vs. 3.52 ± 2.17 years, p=0.040) Age (years) 6.92 ± 3.20 years vs. 6.05 ± 3.15, p>0.05) Gender (male/female) 8/22 vs. 8/59 p>0.05 Micro-organism isolated (*E.coli* /non-*E.coli*) 25/5 vs. 56/11 p>0.05 Follow-up period 3.88 ± 1.97 vs. 3.07 ± 1.86 p>0.05	Only data relevant to the predictors of recurrence was used from this study.

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
Kropp KA;Cichocki GA;Bansal NK; 1978 Oct [212]	Study Type: Cohort Evidence level: 2-	To investigate the relationship between pinworm infestation and in introital cultures in children with recurrent UTI and those without UTI.	41 girls with recurrent UTI compared to 58 age-matched controls	Cases - 40 girls (mean age 5.5 years) referred for evaluation of at least 2 recurrent urinary tract infections documented by culture. Controls - 62 girls with no history of urinary, vaginal or pinworm infections, seen at a walk-in clinic. Exclusions - one girl in the control group had asymptomatic UTI and was included as a case for analysis. Three scotch tape tests were lost or uninterpretable in the control group and were excluded leaving	Scotch tape test introital swab (at the level of the hymenal ring) Mid-stream urine sample taken	Outcome Measures: Positive scotch tape test Introital enterics urine sample positive	9/41 (22%) with recurrent UTI had a positive scotch tape test compared to 3/58 (5%) of controls 31/41 (75%) of girls with recurrent UTI had a positive introital enterics culture compared to 25/58 (43%) of controls	Patient characteristics not presented, so unclear whether groups are comparable. Causal relationship assumed No statistical analysis attempted.

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients	Population Characteristics	Interventions	Outcome measures	Results & Comments	Reviewer Comment
				58 in the control group and 41 in the case group				

1

Antibiotic prophylaxis

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Williams GJ;Lee A;Craig JC; 2001 214	Study Type: Systematic review - meta-analysis Evidence level: 1++	Children under 18 years of age who were at risk of recurrence were included.	Four studies met the inclusion criteria. Trial participants were mostly females aged between six months and 14 years. Three trials investigated antibiotics vs. placebo in children with recurrent UTIs and normal renal tracts from 10-12 weeks One trial compared the effectiveness of nitrofurantoin with trimethoprim over a 6 month period. Brendstrup 1009 Study design: RCT with 6 months follow-up. Participants: 4 boys, 126 girls with a mean age of 7.5 (range 1 to 14 years) UTI: Children with UTI in the previous year. 30 had VUR and 30 had abnormality. Interventions: Nitrofurantoin for 6 months. Trimethoprim for 6 months. Outcomes: Number of repeat infections, adverse events Savage 1975 Study design: Randomised open study, no blinding, follow up 6 months. Participants: Girls aged 5 to 7 years 10 months. UTI: Proven UTI (three consecutive urine samples) 19 had VUR.	Intervention: Long-term antibiotics vs. placebo and studies that compared two or more antibiotic regimens. Long-term prophylaxis was defined as antibiotic administered daily for a period of at least two months. Comparison: Antibiotic vs. placebo	Follow-up period: Outcome Measures: Primary outcomes Number of children with repeat symptomatic UTI (confirmed by bacterial growth in the urine) Recurrent UTI (defined as repeat UTI caused by different bacteria to the initial infection) Secondary outcomes Total number of symptomatic recurrent UTIs	Antibiotic vs. placebo, outcome risk of recurrent UTI Compared to placebo, antibiotics reduced the risk of recurrent UTI (RR 0.36, 95%CI 0.16 to 0.77; RD -46%, 95%CI -59% to -33%) There were no significant differences in the rate of recurrent UTI in control groups (chi2 = 1.29, df = 2, p=0.52) Overall recurrent UTI rate in the placebo group 48/76 (63%), and in the treatment group 15/75 (20%). No reported antibiotic side effects or hospitalisation with recurrent UTI. Antibiotic vs. placebo, outcome quality of the studies Compared to placebo, antibiotics reduced the risk of recurrent UTI in two studies where allocation concealment was unclear or inadequate with no blinding (RR 0.42, 95%CI 0.26 to 0.67; RD -40%, 95%CI -58% to -23%). Risk of recurrent UTI reduced when allocation concealment was adequate with double blinding (RR 0.04, 95%CI 0.0 to 0.67; RD -54%, 95%CI -75% to -34%)	Methodological quality of the trials was poor. One trial had inadequate allocation concealment, two did not state the method of randomisation, and two used no blinding at all. None of the studies used intention-to-treat analysis.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
			Interventions: Nitrofurantoin for 10 weeks after acute treatment or Cotrimoxazole twice daily for 10 weeks after acute treatment. Comparison: No treatment for 10 weeks after acute treatment with ampicillin Outcomes: Number of repeat infections Smellie 1978 Study design: Randomised open study, no blinding, follow up 1 year. Participants: 5 boys and 40 girls between 2 and 12 years. UTI: Proven UTI. No children with VUR Interventions: Low dose Cotrimoxazole for 6 to 12 months or Nitrofurantoin for 6 to 12 months. Comparison: No treatment. Outcomes: Number of repeat infections. Stansfield 1975 Study design: Randomised double blinded, follow up 6 months. Participants: 3 boys and 42 girls aged 6 months to 14 years. UTI: Proven UTI (two or consecutive urine samples + pyuria). 10 children had VUR Interventions: Cotrimoxazole for 6 months Comparison: Placebo tablets for 6 months Outcomes: Number of repeat infections.		Adverse reactions to treatment Hospitalisation with UTI UTI with fever	Antibiotic vs. placebo, outcome VUR vs. non-VUR One study reported incidence separately. Compared to placebo, antibiotics reduced the risk of recurrent UTI in children without VUR was (RR 0.43, 95%CI 0.25 to 0.73; RD -39%, 95%CI -58% to -20%). In children with VUR the RD was -52% (95%CI -71% to -35%). Antibiotic duration There was a reduction in the risk of recurrent UTI by antibiotics over placebo if the antibiotic was used for 10 weeks, six months or 12 months. There was a similar risk reduction in recurrent UTIs with nitrofurantoin (40%) or cotrimoxazole (43%). Nitrofurantoin vs. Trimethoprim One study investigated compared the effectiveness of nitrofurantoin with trimethoprim over a 6 month period. Nitrofurantoin was more effective in preventing recurrent UTI than trimethoprim (RR 0.48, 95%CI 0.25 to 0.92; RD -18%, 95%CI -34% to -3%). However, patients receiving nitrofurantoin were three times more likely to discontinue the antibiotic due to side effects (nausea, vomiting or stomach ache) than patients receiving trimethoprim (RR 3.17, 95%CI Side	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						effects of nitrofurantoin may outweigh its prophylactic effects (NNH = 5, 95%CI 3 to 13) compared with trimethoprim (NNT = 5, 95%CI 3 to 33).	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Wheeler DM;Vimalachandra D;Hodson EM;Roy LP;Smith GH;Craig JC; 2004 215	Study Type: Systematic review - meta-analysis Evidence level: 1++	847 children of any age with primary VUR diagnosed by MCUG following a UTI were included in 7 RCTs.	10 studies met the inclusion criteria of the systematic review. Seven trials were included for the review of the guideline. One trial compared prophylaxis with no treatment and is reported in the prophylaxis section of the guideline. Two additional studies compared materials for endoscopic correction of VUR and are outside the scope.	Intervention: Treatments of VUR including surgery (open and endoscopic techniques) and antibiotic prophylaxis of any duration. Comparison:	Follow-up period: Outcome Measures: UTI Renal parehcnymal abnormality	Antibiotic prophylaxis vs. no treatment There was no significant difference between daily antibiotic prophylaxis and no prophylaxis (RR 0.25, 95%CI 0.03 to 1.83) or between three day a week prophylaxis and no prophylaxis (RR 0.46 95%CI 0.10 to 2.00) There were no differences in the risk of renal parenchymal damage between daily antibiotic prophylaxis and no prophylaxis (RR 0.40 95%CI 0.02 to 9.18) or between three day a week prophylaxis and no prophylaxis (RR 0.38 95%CI 0.02 to 8.59).	Birmingham reflux study only enrolled children with dialating reflux (grades 3 to 5). International reflux study only enrolled children with grades 3 to 4 reflux – children with grade 5 were excluded.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Garin EH;Olavarria F;Garcia N;Valenciano B;Campos A;Young L; 2006[60]	Study Type: RCT Evidence level: 1+	Children with VUR (n=113), 55 received prophylaxis, 58 no prophylaxis Children without VUR (n=105), 45 received prophylaxis, 60 no prophylaxis.	Children aged 3 months to 18 years (average 2 years) Inclusion: Documented episode of acute pyelonephritis. Children with fever (>38.5°C), pyuria (<10 white cells per hpf) and significant bacteriuria (>10^5cfu/ml) underwent DMSA 2 to 7 days following diagnosis of UTI. Those with typical acute pyelonephritis findings on DMSA were included. Acute pyelonephritis defined as focal or diffuse areas of decreased DMSA uptake without evidence of cortical loss. Renal scar defined as decreased uptake associated with loss of the contours of the kidney or cortical thinning with decreased volume. Exclusions: Presence of grades 4 or 5 reflux, neurogenic bladder, posterior urethral valves, urinary diversion, bladder diverticulum ureterocele, renal failure and pregnancy. Exit criteria: 2 episodes of pyelonephritis during the year of follow up monitoring, failure to comply with urinary antibiotic prophylaxis and loss to follow-up monitoring.	Intervention: At entry children underwent urinalysis, urine culture, VCUG and renal ultrasound DMSA was obtained at 6 months following febrile UTI. Gentamicin, cefadroxil, cefuroxime, ceftriaxone, or cefotaxime intravenously for 5 to 7 days (standard dose). Oral antibiotics were given to complete a total antibiotic course of 14 days. Children assigned to prophylaxis	Follow up period: One year Outcome measures: frequency of UTIs (recurrence) Renal parenchymal damage	Baseline characteristics similar, no significant differences in the median age or gender. The group with VUR who were randomised to receive prophylaxis had a median age of one year older (3 years vs. 2 years) compared to the other groups, but the difference was not significant. In children with VUR there were no significant differences in the grade of reflux. Rates of spontaneous resolution of VUR after one year were 37.5 (grade I), 12.5% (grade II) and 10.3% (grade III). Resolution rates did not differ between groups. <u>Recurrence</u> The incidence of recurrent UTI following pyelonephritis was 20.1%. 17.5 recurrences occurred within the first three months following pyelonephritis, 17.5% between 3 and 6 months, 12% between 6 and 9 months and 53% between 9 and 12 months. The recurrence of pyelonephritis was small (12/218) compared to children who had a recurrence of cystitis or of asymptomatic bacteriuria (32/218). Of the children not receiving prophylaxis 22.4% with VUR had a recurrence	No intention to treat analysis. Exit criteria stated. Randomisation method not described.

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
				received either TMP/SMX (1-2mg/kg once daily), or nitrofurantoin (1.5mg/kg once daily) for one year. Children were examined at an outpatient clinic at 3 month intervals. VCUG and ultrasound were repeated at one year. Comparison: Antibiotic vs. no antibiotic		compared to 23.3% of children who did not have VUR (p=0.9). Recurrent pyelonephritis was observed in 7 children compared to only one of the children who did not receive prophylaxis (p=0.0291), however in all 7 cases the bacteria showed resistance to the antibiotic used. Of the children receiving prophylaxis, 23.6% with VUR had a recurrence compared to 8.8% of children who did not have VUR. Children with VUR Prophylaxis 0 asymptomatic 6 cystitis 7 pyelonephritis 42 no recurrence No prophylaxis 3 asymptomatic 9 cystitis 1 pyelonephritis 45 no recurrence Children without VUR Prophylaxis 1 asymptomatic 1 cystitis 2 pyelonephritis 41 no recurrence No prophylaxis	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
						4 asymptomatic 8 cystitis 2 pyelonephritis 46 no recurrence <u>Renal scars</u> 13/218 children developed renal scars during the one year follow up period. There were no differences between those with VUR and those without, nor between those receiving prophylaxis compared to no prophylaxis. Children with VUR 5/55 prophylaxis 2/58 no prophylaxis Children without VUR 2/45 prophylaxis 4/60 without prophylaxis No evidence that VUR increased the likelihood of developing renal scars (p=0.99)	

Bibliographic Information	Study Type & Evidence Level	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Craig J; 2002[216]	Study Type: RCT Evidence level: 1+	From 42,000 fetuses screened for renal tract dilatation, 412 newborns with hydronephrosis were eligible, 71 were diagnosed with VUR and 46 were randomised (29 boys, 17 girls)	Children under 3 months old with isolated VUR	Intervention: TMP/SMX (2mg/kg/day as a single dose or placebo. Comparisons: Antibiotic prophylaxis vs. placebo	Follow up period: 3 years Outcome measures: UTI events Renal damage Renal growth GFR	29/46 had grades III to V (12 in the prophylaxis group and 18 in the placebo group) and 17 had reflux less than grade III. 5 children were lost to follow up (3 placebo, 2 antibiotic) 2 children in the placebo group and no children in the prophylaxis group developed a UTI (p=0.2). No child in either group developed renal scarring on DMSA. Renal growth (2.42 cm vs. 2.83 cm p=0.8) and GFR (119 vs. 108mls/min/1.73m2, p=0.3) were no different between the groups. Assuming absolute risk reduction of 30% over three years with long-term antibiotics, 2000 fetuses would need to be screened to detect 20 with renal tract dilatation of whom 3 would have VUR. With treatment over three years with daily antibiotics, 1 episode of UTI would be prevented.	Abstract only Small study numbers

Vesicoureteric reflux

Table 9-1

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Lai SW;Ng KC; 2003 [217]	Study type: Diagnostic Evidence level: III	Inflammatory parameters for the early detection of VUR in children.	149 with acute pyelonephritis - 123 who had MCUG analysed (48 girls and 75 boys)	Children with documented pyelonephritis at a paediatric department. Children with VUR aged 3.1 ± 3.2 years and children without VUR 1.2 ± 1.4 years. Acute pyelonephritis was diagnosed if DMSA revealed abnormal findings.	MCUG compared to inflammatory markers	No. children with VUR on MCUG Fever >37°C CRP level >0.8mg/dl WBC >11000/mm^3 Neutrophil ratio >80%	Children with VUR had a higher temperature (38.48 ± 0.93 vs 39.00 ± 0.98, p=0.0078) higher CRP level (5.60 ± 5.52 vs 9.26 ± 7.38, p=0.0114) and higher Neutrophil ratio (54.7 ± 16.5 vs 68.5 ± 17.3, p=0.0001) <u>CRP level >0.8mg/dl</u> Sensitivity = 88% Specificity = 11% PPV = 28% NPV 71% <u>Temperature >37°C</u> Sensitivity = 94% Specificity = 10% PPV = 29% NPV = 82% <u>WBC >11,000/mm^3</u> Sensitivity = 79% Specificity = 26% PPV = 29% NPV = 77% <u>Neutrophil ratio >80%</u> Sensitivity = 35% Specificity = 94% PPV = 71% NPV = 79%	Fever is potentially not a good marker for VUR - anti-pyretic drugs given at home could falsely limit fever on presentation. Numbers reported in the paper for combinations of inflammatory markers could not be reproduced. These numbers are excluded from the review.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Zamir G;Sakran W;Horowitz Y;Koren A;Miron D; 2004[218]	Study type: Diagnostic Evidence level: II	To assess renal US in the management of young children with first time febrile UTI	255 (63 male, 192 female) children with first time febrile UTI	All children, aged <5 yrs, hospitalised for uncomplicated febrile UTI in a paediatric department from Jan 1999 to Dec 2000 Febrile UTI defined as: SPA any growth; catheter any growth; or midstream, ≥100bacteria/ml and temp ≥ 38.0C	Renal ultrasound (RUS) compared to MCUG	No. with anatomical abnormalities by renal US Sensitivity, specificity, PPV, NPV of RUS v. MCUG for detecting VUR	3/255 (1.2%) with abnormalities: Enlargement of left kidney, 1 child Renal cyst, 1 child Unilateral double collecting system and severe hydronephrosis, 1 child MCUG + - RUS + 7 26 RUS - 36 183 Sensitivity = 16.3% Specificity = 87.6% PPV= 23.5% NPV= 83.2%	

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Nakamura M;Shinozaki T;Taniguchi N;Koibuchi H;Momoi M;Itoh K; 2003 [219]	Study type: Diagnostic Evidence level: III	To evaluate the diagnostic potential of voiding urosonography (VUS) compared with MCUG under identical conditions and to evaluate potential reasons for false-negative VUS results.	34 boys and 22 girls - 111 ureterorenal units (one patient with a single kidney was included).	Boys and girls 1 month to 14 years (mean age 2.3 years) with confirmed UTI and follow-up of previously detected VUR.	Simultaneous MCUG and VUS	No with VUR Levovist concentrations	REVIEWER CALCULATED RESULTS See reviewer comments Diagnosing reflux by VUS (compared to the gold standard MCUG) 1 month to 14 years sensitivity 86% specificity 95% PPV 86% NPV 95% Under 24 months sensitivity 73% specificity 98% PPV 92% NPV 93%	Have not explained statistical methods in the paper. The results section assumes that both testing methods are equivalent and does not report the diagnostic accuracy of VUS compared to MCUG. We report in the results the NCC-calculated standard diagnostic calculations. Patient selection method unknown Blinding not possible because procedures performed simultaneously.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Xhepa R;Bosio M;Manzoni G; 2004 [220]	Study type: Diagnostic Evidence level II	To evaluate the diagnostic efficacy of voiding cystourethrosonography in children.	34 patients (22 with VUCG analysed) 21 males and 13 females between 1995 and 1999.	Children aged 2 months to 14 years (mean age 3.9 years) referred to hospital for investigation of VUR because of documented pyelonephritis.	CS/CUS compared to MCUG	Number of children with VUR	22 patients had 45 kidney-ureter units. Sensitivity = 93% Specificity = 44% PPV = 75% NPV = 78% Authors contacted – 2 children had duplex kidneys, one had a single kidney and 19 had normal kidneys = 45 ureter units in 22 patients.	Over a four year period (1995-1999) 22 children were received CS. Over a one month period (Oct 2000) 12 children received CUS. Patient selection criteria not reported in enough detail. Unsure whether CS and CUS are equivalent. Authors reported most results by ureter units which will overestimate effectiveness.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Hansson S;Dhamey M;Sigstrom O;Sixt R;Stokland E;Wennerstrom M;Jodal U; 2004[221]	Study Type: Diagnostic Evidence Level: Ib	Evaluated the ability of DMSA scintigraphy to predict the presence of dilating VUR in infants with UTI.	303 children (163 boys, 140 girls)	Children seen at the emergency department of a hospital. Boys aged 5 days to 19.9 months (mean age 3.1 months). Girls aged 5 days to 22.6 months (mean age 8.5 months). Children with suspected obstruction on ultrasound were excluded.	DMSA compared to MCUG	Bacteriuria defined as greater than 10^5 cfu/ml on bag, midstream or catheter sample. Renal damage on urography was defined as focal parenchymal reduction with corresponding calix deformation and/or small kidney.	VUR was present in 36/163 (22%) of boys and 44/140 (31%) of girls. At the primary examination 156/303 (55%) of patients had abnormal DMSA. Sensitivity 66% Specificity 54% PPV 40% NPV 82%	

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Calisti A;Perrotta ML;Oriolo L;Ingianna D;Sciortino R; 2005 Oct[223]	Study Type: Diagnostic Evidence Level: III	To evaluate the impact of imaging techniques in the diagnostic workup and clinical management of a population of children who had a normal renal ultrasound in their fetal life and who were admitted within 24 months for a first episode of UTI.	147 children (71 boys, 76 girls)	Children aged 1 to 24 months who presented between January 2000 and December 2003 with a first time UTI following negative prenatal ultrasound for VUR. UTI defined as >10^5cfu/ml of a single Gram-negative organism, pyuria (>10wbc) and rectal temperature of >38C	A renal ultrasound (RUS) was performed on all children by the same sonographer. MCUG was performed on all children and VUR was graded according to International reflux study committee.	RUS included measurements of renal size, pelvi-calyceal and ureteric diameters before and after micturition. MCUG grade	Renal Ultrasound Sensitivity: 45% Specificity: 30% PPV: 21% NPV: 54% LR: 0.6 DMSA Sensitivity: 63% Specificity: 11% PPV: 60% NPV: 12% LR: 0.71	Unable to match text with calculated numbers. Numebrs presented in text reported. NCC-WCH calculations as follows sensitivity: 58% specificity: 70% PPV: 46% NPV: 79% LR: 1.9

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Sukan A;Bayazit AK;Kibar M;Noyan A;Soyupak S;Yapar Z;Anarat A; 2003 [222]	Study type: Diagnostic Evidence level III-	To compare direct radionuclide cystography and MCUG in children with suspected reflux.	25 children with recurrent UTI (13 female, 12 male)	Children on bacterial prophylaxis, aged 1.5 months to 15 yrs, from May 2000 to Jan 2001	To compare DRNC with MCUG in detection of VUR	No with VUR	MCUG + - DRNC + 1 5 - 4 14 Reviewer calculated results Sensitivity = 20% Specificity= 73.7%	One child unaccounted for and reason not explained in text Sensitivity and specificity calculated by authors (71% and 67% respectively) did not match that calculated at NCC-WCH (either by child or by ureter units) although the same numbers that were reported in the results were used. Authors reported most results by ureter units which will overestimate effectiveness.

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3 **Predicting renal parenchymal defects**

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Prat C;Dominguez J;Rodrigo C;Gimenez M;Azuara M;Jimenez O;Gali N;Ausina V; 2003 May [224]	Diagnostic study Evidence level III-	To test the usefulness of PCT concentration in serum to distinguish between uncomplicated UTI and severe acute pyelonephritis with renal scars.	77 children (number of boys and girls unknown)	Children 1 month to 12 years old admitted to a paediatric emergency department with clinical signs (fever and abdominal pain in older children) and non-specific signs (irritability or vomiting in younger children) and a positive urine sample. Antibiotic therapy was initiated after laboratory samples were taken. Definition of a positive urine sample: ≥10^5cfu/ml in midstream clean voided urine, ≥10^4cfu/ml catherer samples, ≥10^2 in SPA samples. Exclusions: history of UTI or recurrent	PCT concentration, CRP and leukocyte count (on admission) compared to DMSA (performed at 5-6 months)	To establish a range of normal PCT values in a paediatric population, serum samples were obtained from a group of 38 healthy children who had been admitted to hospital for elective surgery. PCT measured by immunoglobulin assay. Scars on DMSA	The area under the ROC curve obtained for PCT in distinguishing between UTI with and without renal damage was 0.83, for CRP 0.72 and for leukocyte count was 0.62. Using a cut-off value of 1ng/ml for PCT Sensitivity 92.3% Specificity 61.9% PPV 32% NPV 97.5% Using a cut-off value of 20mg/l for CRP Sensitivity 92.3% Specificity 34.4% PPV 23% NPV 95%	Study did not provide numbers so no sensitivities/specificities could be checked. Evidence level - so should be excluded if other quality studies are found. The aim of this study was not to localise UTI, but to predict renal scarring.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
				UTI.				

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Hitzel A;Liard A;Dacher JN;Gardin I;Menard JF;Manrique A;Vera P; 2004 Feb [225]	Study Type: Diagnostic Evidence Level: III	To evaluate a quantitative method based on DMSA performed during the acute phase to predict renal scarring. (Authors wanted to improve the positive predictive value for acute-stage DMSA by using a quantitative method based on DMSA.)	43 children (85 kidneys - one child had a single kidney), 3 boys and 40 girls.	Children aged 11 months to 15.5 years (mean 5.8 ± 3.6 years) with acute pyelonephritis and who had DMSA performed at acute stage. Diagnosis of acute pyelonephritis included abdominal or lumbar fossa pain; fever >38°C; positive urine culture (>10 wbc/mm^3 and bacteriuria of 10^4cfu/ml). Exclusions: urinary tract obstruction, VUR grade 3 or higher, or breakthrough infection between inclusion and follow-up.	DMSA (performed at the acute stage)	Kidneys were divided into thirds and graded 0 (no uptake) to 3 (normal uptake). The sum of the three scores was calculated. Scores of ≥7 indicated normal kidneys and scores <7 indicated scarred kidneys <u>Semiquantitative analysis</u> ≥7 on DMSA one and ≥7 on DMSA two = unchanged/normal. <7 on DMSA one and improved by 2 or more points on DMSA two = abnormal improved.	Semiquantitative analysis On DMSA one 59 kidneys = ≥7 26 kidneys = <7 On DMSA two 59 kidneys remained = ≥7 14 kidneys <7 improved by 2 points 12 kidneys <7 improved by less than 2 points. Quantitative analysis The separation of the 3 groups was better using the intensity/severity ratois than with the extent/size ratios. A C70% threshold provided the optimal area under an ROC curve for predicting renal scarring was able to differentiate the unimproved kidneys from the improved kidneys (p=0.004), and was also able to differentiate the normal kidneys from the improved (p<0.0001). When the 70% ratio was used a cut off value of 0.45 was able to predict scarring with a sensitivity of 85%, specificity of 78%, PPV of 85% and NPV of 77%. C70% AI 0.42 ± 0.14 AU 0.52 ± 0.09 NU 0.54 ± 0.07	

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
						<7 on DMSA one and improved by less than 2 points on DMSA two = abnormal unimproved. <u>Quantitative analysis</u> An automatic quantitative analysis of DMSA was performed to establish a quantitative method that could help detect kidneys at risk of scarring after acute pyelonephritis. Successive thresholds were automatically applied to the posterior view of each kidney.		

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
						Two types of quantitative parameters were studied both of which were considered for visual interpretation: The extent/size of cortical uptake defect during acute pyelonephritis (number of pixels: Sn%) Intensity/severity (count density: Cn%)		

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Detecting renal parenchymal defects

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Moorthy I;Wheat D;Gordon I; 2004 [226]	Diagnostic study Evidence level II	The use of ultrasonography in the evaluation of renal scarring.	465 patients (930 kidneys) Number of boys and girls unknown	Children aged 3 months to 16 years with proven UTI who presented to a radiology department and who underwent ultrasound and DMSA on the same day at least 3 months after UTI.	Ultrsonography compared to DMSA (both examinations on the same day)	Focal scarring on DMSA: Diffuse or sharp indentation in contour with thinning of cortex; Any shaped defects with loss of renal volume; Degree of photopenia more commonly severe or absent activity. Diffuse scarring on DMSA: Differential function <45% with homogenous uptake. Focal scarring	Focal scarring in Kidneys Sensitivity: 5.2% Specificity: 98.3% PPV: 50% NPV: 75.8% Diffuse scarring in Kidneys Sensitivity: 47.2% Specificity: 91.8% PPV: 60.8% NPV: 86.6%	

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
						on ultrasound: Approximation of sinus echoes to cortical surface with or without underlying calyceal dilatation; Irregularity of cortical outline. Diffuse scarring on ultrasound: global cortical thinning; >10% difference in renal length on prone view.		

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Wang Y;Chiu N;Chen M;Huang J;Chou H;Chiou Y; 2005[227]	Diagnostic study Evidence level III- However can be revised if the author provides answers to queries	To compare the renal parenchymal changes seen on US with DMSA in children with acute pyelonephritis and to explore the possibility of detecting the inflammation of APN with US and correlating it with the risk of scarring.	45 children (31 boys and 14 girls)	Children aged 9 days to 10 years old (mean 1.5 ± 0.2 years, median 0.3 years) with febrile UTI who fulfilled criteria for acute pyelonephritis and underwent initial DMSA.	Ultrasound and laboratory tests (at the time of hospitalisation) compared to DMSA (performed within one week of hospitalisation)	US assessed as abnormal if one of the following features was observed: parenchymal hyperechogenicity, focal lesion with hyperechogenicity or hypoechogenecity, thickening of the renal pelvis wall, or significant enlargement of the kidney length or width compared to the opposite kidney and compared to the normal range for patient age. Acute DMSA: Acute inflammation was indicated if at least one	US for detecting APN Sensitivity 49% Specificity 88% PPV 91% NPV 40% (p<0.005, OR 7.1, 95%CI 2.18 to 24.41) CRP >70mg/L for detecting APN Sensitivity 59% Specificity 61% PPV 59% NPV 61% (p=0.13, OR 2.2, 95%CI 0.78 to 6.18) US and CRP combined for detecting APN Sensitivity 36% Specificity 95% PPV 95% NPV 36% (p<0.005, OR 11.9, 95%CI 2.15 to 65.72) US for predicting scarring Sensitivity 59% Specificity 61% PPV 59% NPV 61% (p=0.11, OR 2.3, 95% CI 0.82 to 7.65) CRP >70mg/L for predicting scarring Sensitivity 81% Specificity 74% PPV 78% NPV 77%	THIS STUDY SHOULD BE INTERPRETED WITH EXTREME CAUTION. The effects of bias in this study are unknown. Loss to follow up is not explained - for the CRP and low/high risk groups, n=80 where in the US group n=90. Similarly for the follow up DMSA to predict scarring 65 abnormal kidneys were analysed for US while n=58 for CRP and low/high risk groups. This represents more than 10% loss to follow up. The author has been contacted to clarify this.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
						area of decreased focal or diffuse cortical uptake of DMSA was noted with the renal outline preserved. Follow-up DMSA A small whole renal volume and/or deformation of the renal outlines was considered evidence of previous parenchymal injury. If one or more areas of focal renal cortical defects were consistently associated with defects in the renal outline, a renal scar was diagnosed.	(p<0.0001, OR 11.9, 95%CI 3.72 to 38.11) US and CRP combined for predicting scarring Sensitivity 52% Specificity 81% PPV 76% NPV 59% (p<0.01, OR 4.7, 95%CI 1.47 to 14.95)	Only children with abnormal initial DMSA were followed-up. This is potentially misleading in terms of scar formation as there is no comparison group and no potential for the false negatives in the initial group to be recognised. This could over-estimate the effectiveness of the test.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Temiz Y;Tarcan T;Onol FF;Alpay H;Simsek F; 2006 [228]	Diagnostic study Evidence level II	To investigate and compare the efficacy of DMSA and renal ultrasonography in detecting renal scars in children with primary VUR.	62 children (18 boys, 44 girls)	Children aged 6 months to 15 years (mean age 5 years) diagnosed with primary VUR between 1997 and 2003 following a documented UTI. Reflux was bilateral in 29 children and unilateral in 33 children.	DMSA and ultrasound were performed simultaneously.		Of the 90 refluxing units 30 (33%) had grades I to II 37 (41%) had grade III 24 (26%) had grades IV to V DMSA detected renal scars in 32/58 units with bilateral VUR and in 20/33 units with unilateral VUR. Ultrasonography detected scars in 22/58 units with bilateral VUR and in 9/33 with unilateral VUR. Ultrasound did not detect any defects when DMSA was normal. NCC Calculated Unilateral VUR Sensitivity: 69% Specificity: 100% PPV: 100% NPV: 72% Bilateral VUR Sensitivity: 45% Specificity: 100% PPV: 100% NPV: 54%	No information about how tests were carried out, so unlikely to be reproducible.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Kavanagh EC;Ryan S;Awan A;McCourbrey S;O'Connor R;Donoghue V; 2005 [229]	Diagnostic study Evidence level Ib	To compare DMSA with MRI for the detection of renal parenchymal defects in children presenting for radiological investigation after a first UTI.	37 children (19 boys and 18 girls)	Children aged 4 months to 13 years (mean 4.5 years) presenting for radiological investigation at a paediatric hospital after a first UTI. MRI and DMSA were performed at the same appointment. Renal scarring was defined as a photopenic focus and contracted contour on DMSA and as a contracted contour or focal defect on MR sequences.	MRI compared to DMSA (undertaken at the same appointment)	Kidney scarring on a kidney-by-kidney basis where each kidney was graded as normal or abnormal for renal scarring. Kidney scarring on a zonal basis where each kidney was divided into 6 zones and each zone was assessed for the presence or absence of renal scarring..	Scarring on a kidney-by-kidney basis Sensitivity 77% Specificity 87% PPV 77% NPV 87% Scarring on a zonal basis Sensitivity 75% Specificity 98% PPV 83% NPV 97%	Three radiologists reported the MRI results blind to results of the DMSA.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Kovanlikaya A;Okkay N;Cakmakci H;Ozdogan O;Degirmenci B;Kavukcu S; 2004 Jan [230]	Study type: Diagnostic Evidence level: II	To compare MRI and DMSA findings in childhood acute pyelonephritis and to determine pyelonephritic foci in the acute phase.	20 children (15 females, 5 males)	Children aged 2 to 14 years (mean age 7.3 ± 3.4 years) with symptoms of dysuria, enuresis, costovertebral pain, fever of <37.5°C and/or a positive urine culture. Exclusions: elevated levels of serum creatinine, allergy to gadopentate dimeglumine, history of haemolysis and claustrophobia.	MRI compared to DMSA - all children underwent investigations within a week in either order.	Pyelonephritic lesions The kidneys were divided into three zones (upper, mid and lower) Acute pyelonephritis was seen as increased signal areas on enhanced images.	Both MRI and RCS demonstrated evidence of lesions in 11 (55%) patients. Sensitivity 91% Specificity 89% PPV 91% NPV 89% No statistically significant difference in lesion detection according to kidney zones between the two methods (p>0.05)	Small number of children limits the usefulness of this study No definition of a positive urine culture.

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1 Localisation of infection

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Wang Y;Chiu N;Chen M;Huang J;Chou H;Chiou Y; 2005 [227]	Diagnostic study Evidence level III-	To compare the renal parenchymal changes seen on US with DMSA in children with acute pyelonephritis and to explore the possibility of detecting the inflammation of APN with US and correlating it with the risk of scarring.	45 children (31 boys and 14 girls)	Children aged 9 days to 10 years old (mean 1.5 ± 0.2 years, median 0.3 years) with febrile UTI who fulfilled criteria for acute pyelonephritis and underwent initial DMSA.	Detecting scarring: Ultrasound and laboratory tests (at the time of hospitalisation) compared to DMSA (performed within one week of hospitalisation)	US assessed as abnormal if one of the following features was observed: parenchymal hyperechogenicity, focal lesion with hyperechogenicity or hypoechogenecity, thickening of the renal pelvis wall, or significant enlargement of the kidney length or width compared to the opposite kidney and compared to the normal range for patient age. Acute DMSA: Acute	US for detecting APN Sensitivity 49% Specificity 88% PPV 91% NPV 40% (p<0.005, OR 7.1, 95%CI 2.18 to 24.41) CRP >70mg/L for detecting APN Sensitivity 59% Specificity 61% PPV 59% NPV 61% (p=0.13, OR 2.2, 95%CI 0.78 to 6.18) US and CRP combined for detecting APN Sensitivity 36% Specificity 95% PPV 95% NPV 36% (p<0.005, OR 11.9, 95%CI 2.15 to 65.72) US for predicting scarring Sensitivity 59% Specificity 61% PPV 59% NPV 61% (p=0.11, OR 2.3, 95% CI 0.82 to 7.65) CRP >70mg/L for predicting scarring Sensitivity 81%	THIS STUDY SHOULD BE INTERPRETED WITH EXTREME CAUTION. The effects of bias in this study are unknown. Loss to follow up is not explained - for the CRP and low/high risk groups, n=80 where in the US group n=90. Similarly for the follow up DMSA to predict scarring 65 abnormal kidneys were analysed for US while n=58 for CRP and low/high risk groups. This represents more than 10% loss to follow up.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
						inflammation was indicated if at least one area of decreased focal or diffuse cortical uptake of DMSA was noted with the renal outline preserved. Follow-up DMSA A small whole renal volume and/or deformation of the renal outlines was considered evidence of previous parenchymal injury. If one or more areas of focal renal cortical defects were consistently associated with defects in the renal	Specificity 74% PPV 78% NPV 77% (p<0.0001, OR 11.9, 95%CI 3.72 to 38.11) US and CRP combined for predicting scarring Sensitivity 52% Specificity 81% PPV 76% NPV 59% (p<0.01, OR 4.7, 95%CI 1.47 to 14.95)	The author has been contacted to clarify this. Only children with abnormal initial DMSA were followed-up. This is potentially misleading in terms of scar formation as there is no comparison group and no potential for the false negatives in the initial group to be recognised. This could over-estimate the effectiveness of the test..

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
						outline, a renal scar was diagnosed.		

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Ilyas M;Mastin ST;Richard GA; 2002 [231]	Diagnostic study Evidence level III	First, to correlate the clinical and laboratory manifestations of acute pyelonephritis with the results of DMSA in different age groups. Secondly to compare DMSA renal ultrasonography and VCUG, using DMSA as the gold standard.	222 children (47 boys, 175 girls)	Children aged 2 to 228 months (median age 55 months) Group I – 85 children under 2 years old Group II – 91 children 2 to 8 years old Group III – 46 children over 8 years old Acute pyelonephritis defined as fever (≥38ºC), pyuria (positive leukocyte esterase or ≥10wbc/hpf) and positive urine culture (>105cfu/ml) Exclusions: Renal transplant, Obstructive uropathy, neurogenic bladder, renal calculi, recurrent chronic	Renal ultrasound compared to DMSA as gold standard		Group I 41/85 (48%) abnormal DMSA 44/85 (44%) normal DMSA Group II 63/91 (69%) abnormal DMSA 28/91 (31%) normal DMSA Group III 39/46 (85%) abnormal DMSA 7/46 (15%) normal DMSA True positive = 9 False negative = 89 False positive = 0 True negative = 57 Sensitivity: 9% Specificity: 100% PPV: 100% NPV: 39%	Of 163 children, 155 are accounted for in the graph and in the text. Number of false positives not reported in text, however reported in graph as 0. Unsure whether false positive rate is 0 as in graph, or 8 according to text. NCC calculated results, according to numbers in graph.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
				pyelonephritis.				

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Halevy R;Smolkin V;Bykov S;Chervinsky L;Sakran W;Koren A; 2004 [232]	Diagnostic study Evidence level II	To evaluate the ability of power Doppler US (a method of colour Doppler sonography) to detect acute pyelonephritis in infants and young children in comparison with DMSA as a reference standard.	62 children (46 girls and 16 boys)	Children aged 2 weeks to 5 years (mean age 21.7 ± 16.6 months) admitted to a paediatric department with febrile UTI (>38°C) Diagnosis of UTI was any growth on SPA and 10^3 on catheter samples.	On admission blood was sampled for leukocytes, ESR and CRP (before antibiotic therapy). Each child was examined with DMSA and PDU (on the same day) within 3 days of admission.	Abnormalities on DMSA Abnormalities on PDU CRP level ESR Leukocyte WBCs	Group 0-1 (none or mild damage) vs. Group 2-4 acute pyelonephritis, p value. Age in months (22.4 ± 17.2 vs. 20.6 ± 15.3, p=0.66) Gender, female/male (19/7 vs. 23/8, p=0.47 CRP level (48.1 ± 39.2mg/L vs 114.9 ± 48.1mg/L, p<0.001) ESR (32 ± 22mm/hour vs 43 ± 16mm/hour, p=0.46) Leukocyte count, cells/mm^3 (16741 ± 5302 vs. 18492 ± 6839, p=0.1512) White blood cells, $x10^9$/l (14.36 ± 2.9 vs. 16.71 ± 4.1, p=0.06) For detecting acute pyelonephritis, PDU showed: Sensitivity 87% Specificity 92% PPV 93% NPV 86%	No information about blinding. Sampling time period not mentioned.

Bibliographic Information	Study type & Evidence level	Study Aims	Number of patients & prevalence	Population Characteristics	Type of test and Reference standard	Outcome measures	Sensitivity, Specificity, PPV and NPV	Reviewer comment
Bykov S;Chervinsky L;Smolkin V;Halevi R;Garty I; 2003 [233]	Diagnostic study Evidence level Ib	To assess the role of renal power Doppler ultrasonography (PDU) to identify acute pyelonephritis and to determine whether PDU can replace DMSA in the diagnosis of pyelonephritis in children.	40 infants (5 boys and 35 girls)	Children/infants aged 1 to 68 months (mean age 25.9 months) hospitalised with a first episode of high fever and bacteriuria and suspected acute pyelonephritis. Children with abnormalities, hydronephrosis and reflux were excluded Bacteriruia defined as 10^5 cfu/ml from a mid-stream sample or 10^4cfu/ml from a catheter or SPA.	All children were examined with PDU and DMSA within the first 3 days after admission. Investigators were blind to the DMSA outcome	No with abnormalities on PDU No with abnormalities on DMSA	PDU was unobtainable in 2 patients, leaving 78 kidneys available for comparison. PDU compared to DMSA for identifying pyelonephritis. Sensitivity 74% Specificity 94% PPV 87% NPV 87% PDU compared to DMSA for identifying renal lesions in patients with acute pyelonephritis (on DMSA) Sensitivity 58%	

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Surgical intervention for VUR

Bibliographic Information	Study Type & Evidence Level	Study Aim	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
Wheeler DM;Vimalachandra D;Hodson EM;Roy LP;Smith GH;Craig JC; 2004 215	Study Type: Systematic review - meta-analysis Evidence level: 1++	To evaluate the benefits and harms of different treatment options for primary VUR	847 children of any age with primary VUR diagnosed by MCUG following a UTI were included in 7 RCTs.	10 studies met the inclusion criteria of the systematic review. Seven trials were included for the review of the guideline. One trial compared prophylaxis with no treatment and is reported in the prophylaxis section of the guideline. Two additional studies compared materials for endoscopic correction of VUR and are outside the scope.	Intervention: Treatments of VUR including surgery (open and endoscopic techniques) and antibiotic prophylaxis of any duration. Comparison:	Follow-up period: Outcome Measures: UTI Renal parehcnymal abnormality	Antibiotic prophylaxis vs. surgery and antibiotics, outcome UTI Seven trials compared prophylaxis with surgery and antibiotics with the outcomes of UTI. The frequency of recurrent UTI ranged from 0-42% in the antibiotic only group and from 20-22% in the surgery and antibiotic group. By two years there was no reduction in the risk of UTI in the surgery and antibiotic vs. the antibiotic only group (RR1.07, 95%CI 0.55 to 2.09). By five years there was no significant differences in the	Birmingham reflux study only enrolled children with dialating reflux (grades 3 to 5). International reflux study only enrolled children with grades 3 to 4 reflux – children with grade 5 were excluded.

Bibliographic Information	Study Type & Evidence Level	Study Aim	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
							risk of UTI between the groups (RR 0.99, 95%CI 0.79 to 1.26) The risk of febrile UTI reported by the European and USA arms of the International reflux study was significantly lower in the surgery and antibiotic groups (8-10%) than in the antibiotic only groups (22%) (RR 0.43, 95%CI 0.27 to 0.70). The overall incidence of symptomatic UTI (reported only by the European arm) showed no significant difference between the groups (RR 0.95, 95%CI 0.67 to 1.35) Antibiotic prophylaxis vs. surgery and antibiotics, outcome renal	

Bibliographic Information	Study Type & Evidence Level	Study Aim	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
							parenchymal abnormality Seven trials compared prophylaxis with surgery and antibiotics with the outcomes of renal parenchymal abnormality. (see table in text) The risk of renal parenchymal abnormality at 5 years using DMSA was investigated in the European arm of the International Reflux study where no differences were found between the antibiotic group and the surgery and antibiotic group (RR 0.97 95%CI 0.58 to 1.62). The European and US arms of the International Reflux study differentiated between renal scarring and renal	

Bibliographic Information	Study Type & Evidence Level	Study Aim	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
							parenchymal thinning on IVP. There were no differences at 5 years (RR 1.28 95%CI 0.84 to 1.94) or at 10 years (RR0.90 95%CI 0.46 to 1.75). There was no significant difference between daily antibiotic prophylaxis and no prophylaxis (RR 0.25, 95%CI 0.03 to 1.83) or between three day a week prophylaxis and no prophylaxis (RR 0.46 95%CI 0.10 to 2.00) There were no differences in the risk of renal parenchymal damage between daily antibiotic prophylaxis and no prophylaxis (RR 0.40 95%CI 0.02 to 9.18) or between three day a week	

Bibliographic Information	Study Type & Evidence Level	Study Aim	Number of Patients	Patient Characteristics	Intervention & Comparison	Follow-up & Outcome Measures	Effect Size	Reviewer Comments
							prophylaxis and no prophylaxis (RR 0.38 95%CI 0.02 to 8.59).	

1

Advice

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Intervention	Reviewer Comment
Owen D;Vidal-Alaball J;Mansour M;Bordeaux K;Jones KV;Edwards A; 2003 Oct 237	Study Type: OtherCase-series Evidence Level: 4	To assess parental understanding of UTI in their child and identify any delay perceived in the diagnosis, along with identifying how helpful parents had found any information they had been given	52 parents	Parents of children aged over two years being investigated in one outpatient department following proven UTI between 1998 and 2000. Children were eligible if they had no previous history of renal pathology and had been referred to the outpatient department with proven UTI. All children were new referrals and were at their first clinic visit.	Closed and open questions	Was explanation given about the need to test for UTI? 87% yes, 13% no If so, was the explanation helpful? 83% yes, 17% no Did you receive a leaflet about childhood UTIs? 52% yes, 48% no If so, was the leaflet useful? 100% yes, 0% no Was an explanation given about how to collect urine? 79% yes, 21% no If so was the explanation helpful? 95% yes, 5% no Was it difficult to collect urine? 54% yes, 46% no Which method of urine collection did you prefer or manage? Clean catch 40% Bag 37% Pad 23% Did you receive enough information regarding	Intervention: Semi-structured questionnaire was given to parents at their first attendance	

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Intervention	Reviewer Comment
						possible future illness episodes? 80% yes, 20% no Would you know what to do in the event of a repeat episode of UTI? 89% yes, 11% no From this first episode, who requested a urine sample for testing? GP 71% Hospital on admission 8% Health visitor 2% Nurse practitioner 2% Parents themselves 17% On which visit to the clinic was the urine sample requested? First 37% Second 31% Third 14% Fourth 8% Missing 7% Was the sample taken before starting antibiotics? 84% yes, 16% no Content analysis of the qualitative data identified		

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Intervention	Reviewer Comment
						some key themes -Delays in requesting urine samples. Some parents felt there had been a delay between their child becoming unwell and a urine sample being requested. -Difficulties in collection. Mainly around bag collection methods which some parents said produced unnecessary discomfort for their child, while others felt it was difficult to keep the bag in place. -Information. Some parents were happy with the information they received, however the majority requested more information and more detailed advice. -Empowering. Following the initial event, parents in this study seemed to understand more about the diagnosis and felt in a better position to deal with future episodes of UTI in their children.		

Bibliographic Information	Study Type & Evidence Level	Aim of Study	Number of Patients & Patient Characteristics	Population Characteristics	Outcome measures	Results & Comments	Intervention	Reviewer Comment
						Some parents suggested that their experience taught them what to do in the future. -Organisational problems. A number of parents expressed frustration at organisational aspects in terms of limited GP resources in the weekend, several hospital appointments for investigations and receiving different information from different health care professionals.		

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Excluded studies

Predisposing factors

Reference ID	Bibliographic Information	Reason for rejecting study
[239]	Authors: Fanos V;Verlato G;Matti P;Pizzini C;Maffeis C;. Title: Increased incidence of urinary tract infections in patients with coeliac disease. Journal Name: Pediatric Nephrology. Year: 2002	age range of study participants 3-75 years; could not extract data for only under 16s
[240]	Authors: Golding J;Emmett PM;Rogers IS;. Title: Does breast feeding protect against non-gastric infections?. Journal Name: Early Human Development. Year: 1997	review; non-systematic and no primary data
[241]	Authors: Gottbrath-Flaherty EK;Agrawal R;Thaker V;Patel D;Ghai K;. Title: Urinary tract infections in cocaine-exposed infants. Journal Name: Journal of Perinatology. Year: 1995 May	study design based on hypothesis of higher rates of UTI due to genitourinary tract malformations from prenatal cocaine exposure; outside scope of guideline
[242]	Authors: Grady R;Krieger J;. Title: Urinary tract infection in childhood. Journal Name: Current Opinion in Urology. Year: 2001	review, unsystematic and no primary data
[243]	Authors: Jeena PM;Coovadia HM;Adhikari M;. Title: Probable association between urinary tract infections (UTI) and common diseases of infancy and childhood: a hospital-based study of UTI in Durban, South Africa. Journal Name: Journal of Tropical Pediatrics. Year: 1996 Apr	developing country, observational, retrospective study; weak study design and analysis (e.g. no tests of siginificance); results do not help answer Q6; may be useful for Q7?
[244]	Authors: Kontiokari T;Nuutinen M;Uhari M;. Title: Dietary factors affecting susceptibility to urinary tract infection. Journal Name: Pediatric Nephrology. Year: 2004	review, but not systematic and no primary data
[245]	Authors: Lohr JA;. Title: The foreskin and urinary tract infections. Journal Name: Journal of Pediatrics. Year:	commentary/review (unsystematic)
[246]	Authors: Nussinovitch M;Finkelstein Y;Klinger G;Kauschansky A;Volovitz B;Varsano I;. Title: Increased prevalence of urinary tract infections and anomalies in infants with pyloric stenosis. Journal Name: Scandinavian Journal of Urology and Nephrology. Year: 1998 Dec	study design and analysis based on hypothesis of higher rates of UTI due to renal or urinary tract anomalies associated with pyloric stenosis; outside scope of guideline
[247]	Authors: Roberts JA;. Title: Factors predisposing to urinary tract infections in children. Journal Name: Pediatric Nephrology. Year: 1996	Non-systematic review article
[248]	Authors: Saalman R;Fallstrom SP;. Title: High incidence of urinary tract infection in patients with coeliac disease. Journal Name: Archives of Disease in Childhood. Year: 1996 Feb	age range of children included 8 months to 18 years.
[249]	Authors: Singh-Naz N;Sprague BM;Patel KM;Pollack MM;. Title: Risk factors for nosocomial infection in critically ill children: A prospective cohort study. Journal Name: Critical Care Medicine. Year: 1996	children in ICU beyond scope of GL
[250]	Authors: Johnson KE;Rodgers S;. Title: When cultural practices are health risks: the dilemma of female circumcision. Journal Name: Holistic Nursing Practice. Year: 1994 Jan	review/commentary; no primary data reported

Reference ID	Bibliographic Information	Reason for rejecting study
[251]	Authors: Milas V;Milas J;Puseljic S;Gardasanic J;Vukovic D;Milas J;. Title: Clinical importance of significant asimptomatic bacteriuria in newborns and infants during early postnatal period. Journal Name: Collegium Antropologicum. Year: 2004 Dec	No data relevant to UTI in children
[252]	Authors: Moses S;Bailey RC;Ronald AR;. Title: Male circumcision: assessment of health benefits and risks.. Journal Name: Sexually Transmitted Infections. Year: 1998 Oct	unsystematic review with no primary data; adult population
[253]	Authors: Niku SD;Stock JA;Kaplan GW;. Title: Neonatal circumcision.. Journal Name: Urologic Clinics of North America. Year: 1995 Feb	non-systematic review, no primary data
[254]	Authors: Oostenbrink R;van der Heijden AJ;Moons KG;Moll HA;. Title: Prediction of vesico-ureteric reflux in childhood urinary tract infection: a multivariate approach. Journal Name: Acta Paediatrica. Year: 2000 Jul	use for Q7, signs and symptoms
[255]	Authors: Ramirez SP;Hsu SI;McClellan W;. Title: Low body weight is a risk factor for proteinuria in multiracial Southeast Asian pediatric population. Journal Name: American Journal of Kidney Diseases. Year: 2001 Nov	no data on UTI
[256]	Authors: Rushton HG;Majd M;. Title: Pyelonephritis in male infants: How important is the foreskin?. Journal Name: Journal of Urology. Year: 1992	case-control study. does not specify if first time UTI; no 95% CI reported for Ors
[205]	Authors: Shaikh N;Hoberman A;Wise B;Kurs-Lasky M;Kearney D;Naylor S;Haralam MA;Colborn DK;Docimo SG;. Title: Dysfunctional elimination syndrome: is it related to urinary tract infection or vesicoureteral reflux diagnosed early in Life?. Journal Name: Pediatrics. Year: 2003	Among children with UTI data is combined for those with first time and recurrent UTI; Data is reported separately for recurrence, but not analysed for first time UTI.
[257]	Authors: Twaij M;. Title: Urinary tract infection in children: A review of its pathogenesis and risk factors. Journal Name: Journal of the Royal Society for the Promotion of Health. Year: 2000	review, not systematic and no primary data
[258]	Authors: Wijesinha SS;Atkins BL;Dudley NE;Tam PK;. Title: Does circumcision alter the periurethral bacterial flora?. Journal Name: Pediatric Surgery International. Year: 1998 Mar	Study to ascertain whether circumcision affects bacterial flora on glans penis, does not include any diagnosis of UTI
[259]	Authors: Aggarwal VK;Verrier JK;. Title: Vesicoureteric reflux: screening of first degree relatives. Journal Name: Archives of Disease in Childhood. Year: 1989 Nov	Does not investigate or report on UTI
[260]	Authors: Albarus MH;Salzano FM;Goldraich NP;. Title: Genetic markers and acute febrile urinary tract infection in the 1st year of life. Journal Name: Pediatric Nephrology. Year: 1997	Does not specify whether children investigated had previous UTI or not
[261]	Authors: Barroso JU;Barroso DV;Jacobino M;Vinhaes AJ;Macedo JA;Srougi M;. Title: Etiology of urinary tract infection in scholar children. Journal Name: International Braz J Urol. Year: 2003	does not specify first time UTI in population of children 3- 14 yrs old; possibly useful for Q7 on signs and symptoms
[262]	Authors: Canning DA;. Title: Cohort study on circumcision of newborn boys and subsequent risk of urinary-tract infection. Journal Name: Journal of Urology. Year: 1999 Oct	primary data presented in [263]; already included in GL
[264]	Authors: Chessare JB;. Title: Circumcision: Is the risk of urinary tract infection really the pivotal issue?. Journal Name: Clinical Pediatrics. Year: 1992	decision tree to help parents decide on circumcision; no primary data and not relevant for circumcision as risk factor for UTI
[265]	Authors: Cohen HA;Drucker MM;Vainer S;Ashkenasi A;Amir J;Frydman M;Varsano I;. Title: Postcircumcision urinary tract infection. Journal Name: Clinical Pediatrics. Year: 1992 Jun	Does not specify if analysis is based on first episode of UTI only or if recurrent cases are included

Reference ID	Bibliographic Information	Reason for rejecting study
[266]	Authors: Fujita K;Mizuno T;Ushiyama T;Suzuki K;Hadano S;Satoh S;Kambayashi T;Mugiya S;Nakano M;. Title: Complicating risk factors for pyelonephritis after extracorporeal shock wave lithotripsy. Journal Name: International Journal of Urology. Year: 2000 Jun	Adult population
[267]	Authors: Goldman M;Barr J;Bistritzer T;Aladjem M;. Title: Urinary tract infection following ritual Jewish circumcision. Journal Name: Israel Journal of Medical Sciences. Year: 1996 Nov	Does not specify whether first or recurrent UTI
[268]	Authors: Grio R;Porpiglia M;Vetro E;Uligini R;Piacentino R;Mini D;Marchino GL;. Title: Asymptomatic bacteriuria in pregnancy: maternal and fetal complications. Journal Name: Panminerva Medica. Year: 1994 Dec	Pregnant population; no primary data
[269]	Authors: Harel L;Straussbergr R;Jackson S;Amir J;Tiqwa P;. Title: Influence of circumcision technique on frequency of urinary tract infections in neonates. Journal Name: Pediatric Infectious Disease Journal. Year: 2002 Sep	Does not specify if analysis is based on first episode of UTI only or if recurrent cases are included
[270]	Authors: Asharam K;Bhimma R;Adhikari M;. Title: Human immunodeficiency virus and urinary tract infections in children. Journal Name: Annals of Tropical Paediatrics. Year: 2003	Immunosuppresed children are outside the scope of the guideline
[271]	Authors: Bonnin F;Lottmann H;Sauty L;Garel C;Archambaud F;Baudouin V;El GA;Loirat C;Bok BD;Aigrain Y;. Title: Scintigraphic screening for renal damage in siblings of children with symptomatic primary vesico-ureteric reflux.[see comment]. Journal Name: BJU International. Year: 2001 Apr	Does not investigate VUR in relation to UTI
[128]	Authors: Nayir A;. Title: Circumcision for the prevention of significant bacteriuria in boys. Journal Name: Pediatric Nephrology. Year: 2001 Dec	Recruited at first UTI and followed for recurrence; may be good for Q7, signs and symptoms
[272]	Authors: Pierce AM;Hart CA;. Title: Vulvovaginitis: causes and management.[see comment]. Journal Name: Archives of Disease in Childhood. Year: 1992 Apr	Investigates association between bacteriuria and vulvovaginitis without specifying or defining consequent UTI
[273]	Authors: Gorelick MH;Shaw KN;. Title: Clinical decision rule to identify febrile young girls at risk for urinary tract infection. Journal Name: Archives of Pediatrics & Adolescent Medicine. Year: 2000	Does not specify first time UTI or if recurrent cases are included
[274]	Authors: Hansson S;Jodal U;Lincoln K;Svanborg EC;. Title: Untreated asymptomatic bacteriuria in girls: II - Effect of phenoxymethylpencillin and erythromycin given for intercurrent infections. Journal Name: BMJ. Year: 1989	Small study, case-series design, old (1989). Also appears that the 51 girls in the sample all had previous UTI.
[275]	Authors: Kenda RB;Fettich JJ;. Title: Vesicoureteric reflux and renal scars in asymptomatic siblings of children with reflux. Journal Name: Archives of Disease in Childhood. Year: 1992	same data as from Kenda & Fettich, 1997[276] which is already included
[277]	Authors: Noe HN;. Title: The long-term results of prospective sibling reflux screening. Journal Name: Journal of Urology. Year: 1992	Age of included siblings not specified. Site of patient recruitment not specified (i.e., private practice or hospital? tertiary care or primary care?).
[278]	Authors: Noe HN;Wyatt RJ;Peeden JN;Rivas ML;. Title: The transmission of vesicoureteral reflux from parent to child. Journal Name: Journal of Urology. Year: 1992	no data on UTI
[279]	Authors: Peeden JN;Noe HN;. Title: Is it practical to screen for familial vesicoureteral reflux within a private pediatric practice?. Journal Name: Pediatrics. Year: 1992	Investigates VUR as an outcome rather than UTI
[280]	Authors: Pisacane A;Graziano L;Mazzarella G;Scarpellino B;Zona G;. Title: Breast feeding and urinary tract infection. Journal Name: Journal of Pediatrics. Year: 1992	Does not specify if infants were recruited for first time or recurrent UTI

Reference ID	Bibliographic Information	Reason for rejecting study
[281]	Authors: Plos K;Connell H;Jodal U;Marklund BI;Marild S;Wettergren B;Svanborg C;. Title: Intestinal carriage of P fimbriated Escherichia coli and the susceptibility to urinary tract infection in young children. Journal Name: Journal of Infectious Diseases. Year: 1995	Does not specify whether children investigated had previous UTI or not
[282]	Authors: Van den Abbeele AD;Treves ST;Lebowitz RL;Bauer S;David RT;Retik A;Colodny A;. Title: Vesicoureteral reflux in asymptomatic siblings of patients with known reflux: radionuclide cystography. Journal Name: Pediatrics. Year: 1987	Does not specify whether children investigated had previous UTI or not
[283]	Authors: Wiswell TE;Roscelli JD;. Title: Corroborative evidence for the decreased incidence of urinary tract infections in circumcised male infants. Journal Name: Pediatrics. Year: 1986	This study purports to cover longer timeframe for same population as Wiswell et al, 1985[284] but the numbers in this study are smaller and not consistent with those reported in [284].
[285]	Authors: Wiswell TE;Hachey WE;. Title: Urinary tract infections and the uncircumcised state: an update. Journal Name: Clinical Pediatrics. Year: 1993	Primary data studies already included in GL;review included studies of low quality which were excluded from the GL
[286]	Authors: Foxman B;Frerichs RR;. Title: Epidemiology of urinary tract infection: diet, clothing, and urination habits... part 2. Journal Name: American Journal of Public Health. Year:	In adult women aged 16-39

Symptoms and signs

Reference ID	Bibliographic Information	Reason for rejecting study
[287]	Authors: Ahmed SM;Swedlund SK. Title: Evaluation and treatment of urinary tract infections in children. Journal Name: American Family Physician. Year: 1998	non systematic review; no primary data
[288]	Authors: Garcia FJ;Nager AL;. Title: Jaundice as an early diagnostic sign of urinary tract infection in infancy.[see comment]. Journal Name: Pediatrics. Year: 2002 May	Study investigates jaundice as outcome rather than symptom of UTI
[289]	Authors: Heldrich FJ;Barone MA;Spiegler E;. Title: UTI: diagnosis and evaluation in symptomatic pediatric patients.[see comment]. Journal Name: Clinical Pediatrics. Year: 2000 Aug	Study does not report on signs or symptoms of UTI
[290]	Authors: Labbe J;. Title: Self-induced urinary tract infection in school-age boys. Journal Name: Pediatrics. Year: 1990 Nov	outside scope of GL
[291]	Authors: Lee P;Verrier JK;. Title: Urinary tract infection in febrile convulsions. Journal Name: Archives of Disease in Childhood. Year: 1991	The rate of UTI in 43% of children who presented with febrile convulsions is this study is not known; case-series study designed to assess local paediatric approach to diagnosing UTI
[292]	Authors: Loening-Baucke V;. Title: Urinary incontinence and urinary tract infection and their resolution with treatment of chronic constipation of childhood.. Journal Name: Pediatrics. Year: 1997 Aug	Includes children whose age was outside scope of GL and unable to separate data by age group
[293]	Authors: Persad R;Kamineni S;Mouriquand PD;. Title: Recurrent symptoms of urinary tract infection in eight patients with refluxing ureteric stumps. Journal Name: British Journal of Urology. Year: 1994 Dec	To be included in recurrence section
[261]	Authors: Barroso JU;Barroso DV;Jacobino M;Vinhaes AJ;Macedo JA;Srougi M;. Title: Etiology of urinary tract infection in scholar children. Journal Name: International Braz J Urol. Year: 2003	Definition of UTI not reported. No details given about cut-off values or urine collection method.

Reference ID	Bibliographic Information	Reason for rejecting study
[294]	Authors: Dayan PS;Hanson E;Bennett JE;Langsam D;Miller SZ;. Title: Clinical course of urinary tract infections in infants younger than 60 days of age. Journal Name: Pediatric Emergency Care. Year:	Aim of study was to assess the likelihood of progression to illness and speed of fever resolution rather than to document signs & symptoms of UTI
[243]	Authors: Jeena PM;Coovadia HM;Adhikari M;. Title: Probable association between urinary tract infections (UTI) and common diseases of infancy and childhood: a hospital-based study of UTI in Durban, South Africa. Journal Name: Journal of Tropical Pediatrics. Year: 1996 Apr	poor study design; no age range specified, therefore unclear whether patients in sample were within scope of GL
[246]	Authors: Nussinovitch M;Finkelstein Y;Klinger G;Kauschansky A;Volovitz B;Varsano I;. Title: Increased prevalence of urinary tract infections and anomalies in infants with pyloric stenosis. Journal Name: Scandinavian Journal of Urology and Nephrology. Year: 1998 Dec	Retrospective case-series of infants with infantile hypertrophic pyloric stenosis
[295]	Authors: Vachvanichsanong P;Malagon M;Moore ES;. Title: Urinary tract infection in children associated with idiopathic hypercalciuria. Journal Name: Scandinavian Journal of Urology and Nephrology. Year: 2001	Case review using IH as outcome rather than UTI
[296]	Authors: Schneider PF;Riley TV;. Title: Staphylococcus saprophyticus urinary tract infections: Epidemiological data from Western Australia. Journal Name: European Journal of Epidemiology. Year: 1996	Symptoms of UTI not reported.
[43]	Authors: Shaw KN;Gorelick M;McGowan KL;Yakscoe NM;Schwartz JS;. Title: Prevalence of urinary tract infection in febrile young children in the emergency department. Journal Name: Pediatrics. Year: 1998 Aug	Symptoms presented for 2411 children presenting to an emergency department that meet criteria for age, sex and temperature. Not investigating symptoms in children specifically with UTI.

Urine collection

Reference ID	Bibliographic Information	Reason for rejecting study
[297]	Authors: Alam MT;Coulter JBS;Pacheco J;Correia JB;Ribeiro MGB;Coelho MFC;Bunn JEG;. Title: Comparison of urine contamination rates using three different methods of collection: Clean-catch, cotton wool pad and urine bag. Journal Name: Annals of Tropical Paediatrics. Year: 2005	Study specifically excludes children with suspected UTI.
[298]	Authors: BUYS H;. Title: Suprapubic aspiration under ultrasound guidance in children with fever of undiagnosed cause. (Research method of obtaining urine samples from children to test for urinary tract infection). Journal Name: British Medical Journal. Year: 1994	Non-comparative study
[299]	Authors: Centre for Reviews and Dissemination;. Title: Screening tests for urinary tract infection in children: a meta-analysis (Structured abstract). Journal Name: The Cochrane Library. Year: 2005	Structured abstract of meta-analysis that is included in HTA
[300]	Authors: Davies D;. Title: Bag urine specimens still not appropriate in diagnosing urinary tract infections in infants. Journal Name: Canadian Journal of Infectious Diseases. Year: 2004	Review only - no primary data
[301]	Authors: Farrell M;Devine K;Lancaster G;Judd B;. Title: A method comparison study to assess the reliability of urine collection pads as a means of obtaining urine specimens from non-toilet-trained children for microbiological examination. Journal Name: Journal of Advanced Nursing. Year:	Included in HTA

Reference ID	Bibliographic Information	Reason for rejecting study
302	Authors: Feasey S;. Title: Are Newcastle urine collection pads suitable as a means of collecting specimens from infants? (Research on ability of the pads to produce uncontaminated specimens in non-toilet trained children with suspected urinary tract infection. 19 refs). Journal Name: Paediatric Nursing. Year:	Included in HTA
303	Authors: Jodal U;. Title: Suprapubic aspiration of urine in the diagnosis of urinary tract infection in infants. Journal Name: Acta Paediatrica. Year: 2002	Review only - no primary data
304	Authors: Li PS;Ma LC;Wong SN;. Title: Is bag urine culture useful in monitoring urinary tract infection in infants?. Journal Name: Journal of Paediatrics and Child Health. Year: 2002	Selection criteria not explained Unclear time lag between index test and reference standard Only those with a positive index test received the reference standard.
305	Authors: Macfarlane PI;Ellis R;Hughes C;Houghton C;Lord R;. Title: Urine collection pads: Are samples reliable for urine biochemistry and microscopy?. Journal Name: Pediatric Nephrology. Year: 2005	Study in healthy adult volunteers.
306	Authors: Peniakov M;Antonelli J;Naor O;Miron D;. Title: Reduction in contamination of urine samples obtained by in-out catheterization by culturing the later urine stream. Journal Name: Pediatric Emergency Care. Year:	Letter to the Editor
307	Authors: PIERRO A;. Title: A method for urine collection in infants. Journal Name: Archives of Disease in Childhood. Year: 1999	Non-comparative study
308	Authors: Rao S;Houghton C;Macfarlane PI;. Title: A new urine collection method; pad and moisture sensitive alarm [1]. Journal Name: Archives of Disease in Childhood. Year:	Letter only - no primary data
309	Authors: Shvartzman P;Nasri Y;. Title: Urine culture collected from gel-based diapers: developing a novel experimental laboratory method. Journal Name: Journal of the American Board of Family Practice. Year: 2004 Mar	Study does not report age of patients studied, however assume adults because brand of diaper is 'Depend' which manufactures incontinence underwear for the elderly.
310	Authors: Vernon S;. Title: Urine collection from infants: a reliable method. (9 refs). Journal Name: Paediatric Nursing. Year: 1995	Non-comparative study
311	Authors: Burke N;. Title: Alternative methods for newborn urine sample collection. Journal Name: Pediatric Nursing. Year: 1995	Study collects urine samples from newborns in a neonatal intensive care unit.
312	Authors: Feasey S;. Title: Research & commentary: reliability of urine collection pads. Journal Name: Paediatric Nursing. Year: 2002	Commentary only - no primary data
313	Authors: Hutchinson SK;. Title: Obtaining urine specimens from diapers. Journal Name: Journal of the Association of Pediatric Oncology Nurses. Year: 1987	Comment only - no primary data
314	Authors: Kirkpatrick JM;Alexander J;Cain RM;. Title: Recovering urine from diapers: are test results accurate?. Journal Name: MCN: the American Journal of Maternal/Child Nursing. Year: 1997	Recruited healthy children who were part of a research project identifying appropiate levels of calcium in the body.
315	Authors: Lewis J;. Title: Clean-catch versus urine collection pads: a prospective trial. Journal Name: Paediatric Nursing. Year: 1998	Small numbers: 16 samples analysed
316	Authors: Penney S;Andrews W;Levy R;Friel J;. Title: 24-hour urine collection device for low birth weight infants. Journal Name: Neonatal Network: The Journal of Neonatal Nursing. Year: 1993	Non-comparative study. Explains a urine collection device
317	Authors: Raper J;. Title: Commentary on Suprapubic bladder aspiration versus urethral catheterization in ill infants: success, efficiency, and complication rates. Journal Name: ENA'S Nursing Scan in Emergency Care. Year: 1994	Case study on Kawasaki disease

Reference ID	Bibliographic Information	Reason for rejecting study
318	Authors: Reams PK;Deane DM;. Title: Bagged versus diaper urine specimens and laboratory values. Journal Name: Neonatal Network: The Journal of Neonatal Nursing. Year: 1988	Urine collection is pad, over the top of a perforated bag and then samples of each compared. These samples are not independent.
319	Authors: Schlager TA;Dunn ML;Dudley SM;Lohr JA;. Title: Bacterial contamination rate of urine collected in a urine bag from healthy non-toilet-trained male infants. Journal Name: Journal of Pediatrics. Year: 1990	Non-comparative study
320	Authors: Suri S;. Title: Simplifying urine collection from infants and children without losing accuracy. Journal Name: MCN: the American Journal of Maternal/Child Nursing. Year: 1988	Not compared to a reference standard
321	Authors: O'Callaghan C;McDougall PN;. Title: Successful suprapubic aspiration of urine. Journal Name: Archives of Disease in Childhood. Year: 1987	Non-comparative study
322	Authors: Austin BJ;Bollard C;Gunn TR;. Title: Is urethral catheterization a successful alternative to suprapubic aspiration in neonates?. Journal Name: Journal of Paediatrics & Child Health. Year: 1999 Feb	Study conducted in a neonatal intensive care unit - out of scope
323	Authors: Cohen HA;Woloch B;Linder N;Vardi A;Barzilai A;. Title: Urine samples from disposable diapers: an accurate method for urine cultures. Journal Name: Journal of Family Practice. Year: 1997 Mar	Included in the HTA
324	Authors: Falcao MC;Leone CR;D'Andrea RA;Berardi R;Ono NA;Vaz FA;. Title: Urinary tract infection in full-term newborn infants: value of urine culture by bag specimen collection. Journal Name: Revista do Hospital das Clinicas;. Year: 1999 May	Not all children received the reference standard
325	Authors: Murphy BF;Fairley KF;Birch DF;Marshall AC;Durman OB;. Title: Culture of mid catheter urine collected via an open-ended catheter: a reliable guide to bladder bacteriuria. Journal Name: Journal of Urology. Year: 1984 Jan	Adult population
326	Authors: Ramage IJ;Chapman JP;Hollman AS;Elabassi M;McColl JH;Beattie TJ;. Title: Accuracy of clean-catch urine collection in infancy. Journal Name: Journal of Pediatrics. Year: 1999 Dec	Included in the HTA
327	Authors: Rees JC;Vernon S;Pedler SJ;Coulthard MG;. Title: Collection of urine from washed-up potties. Journal Name: Lancet. Year: 1996 Jul	Letter to the editor - no primary data
328	Authors: Tobiansky R;Evans N;. Title: A randomized controlled trial of two methods for collection of sterile urine in neonates. Journal Name: Journal of Paediatrics & Child Health. Year: 1998 Oct	Study recruited neonates who were being investigated for late onset sepsis.
329	Authors: Carley SD;. Title: Best evidence topic report. Clean catch or bag specimen in UTI in non toilet trained children?. Journal Name: Emergency Medicine Journal. Year: 2006 Mar	Non-systematic review.
330	Authors: Garcia-Nieto V;Navarro JF;Sanchez-Almeida E;Garcia-Garcia M;. Title: Standards for ultrasound guidance of suprapubic bladder aspiration. Journal Name: Pediatric Nephrology. Year: 1997	Non-comparative study
331	Authors: Kuzmic AC;Brkljacic B;Ivankovic D;. Title: The impact of bladder shape on the ultrasonographic measurement of bladder volume in children. Journal Name: Pediatric Radiology. Year: 1	Non-comparative study
332	Authors: Mohammed SH;. Title: Suprapubic micturition cystourethrography. Journal Name: Acta Radiologica. Year: 1988	Non-comparative study
333	Authors: Nangia S;. Title: Ultrasound guided suprapubic bladder aspiration. Journal Name: Indian Pediatrics. Year: 1998 Aug	Letter to the editor - no primary data

Reference ID	Bibliographic Information	Reason for rejecting study
[334]	Authors: Roberts KB;. Title: The AAP practice parameter on urinary tract infections in febrile infants and young children. Journal Name: American Family Physician. Year: 2000	Not related to SPA
[335]	Authors: Wright NB;BUYS H;Pead L;Hallett R;Maskell R;. Title: Suprapubic aspiration in children. Use of ultrasound guidance unclear. Journal Name: British Medical Journal. Year: 1994	Letter to the editor - no primary data

Urine preservation

Reference ID	Bibliographic Information	Reason for rejecting study
[336]	Authors: Dorn GL;. Title: Microbial stabilization of antibiotic-containing urine samples by using the FLORA-STAT urine transport system. Journal Name: Journal of Clinical Microbiology. Year: 1991	Flora-stat system not available in the UK
[337]	Authors: Pearson JC;Kromhout L;King EB;. Title: Evaluation of collection and preservation techniques for urinary cytology. Journal Name: Acta Cytologica. Year: 1981 May	Not in humans
[338]	Authors: Beyer-Boon ME;Arentz PW;Kirk RS;. Title: A comparison of thiomersal and 50% alcohol as preservatives in urinary cytology. Journal Name: Journal of Clinical Pathology. Year: 1979 Feb	In patients with urinary carcinoma
[339]	Authors: Horton JA;Kirshblum SC;Linsenmeyer TA;Johnston M;Rustagi A;. Title: Does refrigeration of urine alter culture results in hospitalized patients with neurogenic bladders?. Journal Name: Journal of Spinal Cord Medicine. Year: 1998	Only in patients with neurogenic bladders. Includes asymptomatic patients.

Urine testing

Reference ID	Bibliographic Information	Reason for rejecting study
[340]	Authors: Aliyu SH;Ludlum H;Abubakar I;Bentley N;. Title: What is the role of urine dipstick testing in the management of UTI?. Journal Name: British Journal of General Practice. Year: 2002 May	Review - no primary data
[341]	Authors: Arya SC;. Title: Dipstick urinalysis and the accuracy of the clinical diagnosis of urinary tract infection.. Journal Name: Journal of Emergency Medicine. Year: 2002 Jan	Review not primary data
[342]	Authors: Barry H;. Title: What clinical variables predict the presence of a urinary tract infection in febrile young girls aged younger than 2 years?. Journal Name: Evidence-Based Practice. Year: -32676	Not about urine testing - Included in predictive factors section
[343]	Authors: Bjerrum L;Grinsted P;Sogaard P;. Title: Can we rely on the results of urine microscopy and culture when tests are performed in general practice?. Journal Name: Ugeskrift for Laeger. Year: 2002	Foreign language - not correct question
[344]	Authors: Blom M;Sorensen TL;Espersen F;Frimodt-Moller N;. Title: Validation of FLEXICULT SSI-Urinary Kit for use in the primary health care setting. Journal Name: Scandinavian Journal of Infectious Diseases. Year: 2002	Study to test susceptibility of bacteria to antimicrobials.

Reference ID	Bibliographic Information	Reason for rejecting study
345	Authors: Buchsbaum GM;Albushies DT;Guzick DS;. Title: Utility of urine reagent strip in screening women with incontinence for urinary tract infection. Journal Name: International Urogynecology Journal. Year: 2004 Nov	Study in adult women with incontinence
346	Authors: Butani RC;Shaffer RT;Szyjkowski RD;Weeks BE;Speights LG;Kadakia SC;. Title: Rapid diagnosis of infected ascitic fluid using leukocyte esterase dipstick testing. Journal Name: American Journal of Gastroenterology. Year: 2004 Mar	Not looking at diagnosis of UTI
347	Authors: Church D;Gregson D;. Title: Screening urine samples for significant bacteriuria in the clinical microbiology laboratory. Journal Name: Clinical Microbiology Newsletter. Year: 2004	Reviwe only - no primary data
348	Authors: Eidelman Y;Raveh D;Yinnon AM;Ballin J;Rudensky B;Gottehrer NP;. Title: Reagent strip diagnosis of UTI in a high-risk population. Journal Name: American Journal of Emergency Medicine. Year: 2002	Adults with a mean age of 78 years.
349	Authors: Frimodt-Moller N;. Title: Can urine microscopy be trusted?. Journal Name: Ugeskrift for Laeger. Year: 2002	Not in English
350	Authors: Fuchs PC;. Title: Urine culture. Journal Name: MLO: Medical Laboratory Observer. Year: 1993	Comments only not primary study
351	Authors: Harkless GH;. Title: A clear urine specimen on visual inspection cannot totally exclude a diagnosis of urinary tract infection.. Journal Name: Evidence-Based Nursing. Year: 2001	Summary of study included in HTA
352	Authors: Herr SM;Wald ER;Pitetti RD;Choi SS;. Title: Enhanced urinalysis improves identification of febrile infants ages 60 days and younger at low risk for serious bacterial illness. Journal Name: Pediatrics. Year: 2001	Not looking at diagnosis of UTI
353	Authors: Hinata N;Shirakawa T;Okada H;Shigemum K;Kamidono S;Gotoh A;. Title: Quantitative detection of Escherichia coli from urine of patients with bacteriuria by real-time PCR. Journal Name: Molecular Diagnosis. Year: 2004	Does not look at urine testing but at tests to identify different bacteria
354	Authors: Isaacman DJ;Burke BL;. Title: Utility of the serum C-reactive protein for detection of occult bacterial infection in children. Journal Name: Archives of Pediatrics & Adolescent Medicine. Year: 2002	Not looking at urine testing for UTI
355	Authors: Jortani SA;Pugia MJ;Elin RJ;Thomas M;Womack EP;Cast T;Valdes JR;. Title: Sensitive noninvasive marker for the diagnosis of probable bacterial or viral infection. Journal Name: Journal of Clinical Laboratory Analysis. Year: 2004	Wrong test - urinary trypsin inhibitor
356	Authors: Klaschik S;Lehmann LE;Raadts A;Book M;Hoeft A;Stuber F;. Title: Real-time PCR for detection and differentiation of gram-positive and gram-negative bacteria.. Journal Name: Journal of Clinical Microbiology. Year: 2002 Nov	Does not look at urine testing but at tests to identify different bacteria
357	Authors: Koken T;Aktepe OC;Serteser M;Samli M;Kahraman A;Dogan N;. Title: Determination of cut-off values for leucocytes and bacteria for urine flow cytometer (UF-100) in urinary tract infections. Journal Name: International Urology & Nephrology. Year: 2002	Don't know age of patients. Assume adults since participants asked to use a sterile wet tissue before provding clean catch sample.
358	Authors: Lammers RL;Gibson S;Kovacs D;Sears W;Strachan G;. Title: Comparison of test characteristics of urine dipstick and urinalysis at various test cutoff points. Journal Name: Annals of Emergency Medicine. Year: 2001	In women with dysuria, urgency or urinary frequency
359	Authors: Monane M;Gurwitz JH;Lipsitz LA;Glynn RJ;Choodnovskiy I;Avorn J;. Title: Epidemiologic and diagnostic aspects of bacteriuria: a longitudinal study in	Adult population

Reference ID	Bibliographic Information	Reason for rejecting study
	older women. Journal Name: Journal of the American Geriatrics Society. Year: 1995	
[360]	Authors: Perry JD;Butterworth LA;Nicholson A;Appleby MR;Orr KE;. Title: Evaluation of a new chromogenic medium, Uriselect 4, for the isolation and identification of urinary tract pathogens. Journal Name: Journal of Clinical Pathology. Year: 2003 Jul	Does not look at urine testing but at tests to identify different bacteria
[361]	Authors: Pewitt EB;Schaeffer AJ;. Title: Urinary tract infection in urology, including acute and chronic prostatitis. Journal Name: Infectious Disease Clinics of North America. Year: 1997	Case series in adults
[362]	Authors: Pugia MJ;Sommer R;Corey P;Anderson L;Gleason S;Jortani SA;Elin RJ;Gopual DL;Valdes R;Lott JA;. Title: The uristatin dipstick is useful in distinguishing upper respiratory from urinary tract infections. Journal Name: Clinica Chimica Acta. Year: 2004 Mar	Not urine testing accuracy for UTI
[363]	Authors: Rahn DD;Boreham MK;Allen KE;Nihira MA;Schaffer JI;. Title: Predicting bacteriuria in urogynecology patients. Journal Name: American Journal of Obstetrics and Gynecology. Year: 2005	In women with urogynaecological problems.
[364]	Authors: Rehmani R;. Title: Accuracy of urine dipstick to predict urinary tract infections in an emergency department. Journal Name: Journal of Ayub Medical College. Year: 2004	In adult patients.
[365]	Authors: Sharief N;Hameed M;Petts D;. Title: Use of rapid dipstick tests to exclude urinary tract infection in children... reprinted from the British Journal of Biomedical Science 1988;55:242-246. Journal Name: Journal of Continuing Education Topics & Issues. Year:	Included in the HTA
[366]	Authors: Simerville JA;Maxted WC;Pahira JJ;. Title: Urinalysis: a comprehensive review.. Journal Name: American Family Physician. Year: 2005 Mar 15	Non systamtic review
[367]	Authors: Stauss J;Connolly LP;Perez-Rossello J;Treves ST;. Title: Pediatric acute pyelonephritis: diagnosis facilitated by skeletal scintigraphy. Journal Name: Clinical Nuclear Medicine. Year: 2003 Oct	One case described only
[368]	Authors: Stephens MB;Wilder L;. Title: Is screening urinalysis in children worthwhile?. Journal Name: Journal of Family Practice. Year: 2003	Review - not primary data
[369]	Authors: Thayyil S;Shenoy M;Hamaluba M;Gupta A;Frater J;Verber IG;. Title: Is procalcitonin useful in early diagnosis of serious bacterial infections in children?. Journal Name: Acta Paediatrica. Year: 2005 Feb	Does not look at urine testing for UTI
[370]	Authors: Wald ER;. Title: Evaluating urine cultures in young infants.. Journal Name: Pediatric Infectious Disease Journal. Year: 2004 Apr	Comment only not primary study
[371]	Authors: Wigton RS;. Title: The Uriscreen test was not better than standard urinalysis and dipstick tests for detecting urinary tract infection in children.. Journal Name: ACP Journal Club. Year: 2000	Review/comment of a study - no primary data
[372]	Authors: Wilson ML;Gaido L;. Title: Laboratory diagnosis of urinary tract infections in adult patients.. Journal Name: Clinical Infectious Diseases. Year: 2004 Apr 15	Review - no primary data
[373]	Authors: Wright S;. Title: Review: both Gram stain and urine dipstick analysis were accurate in diagnosing urinary tract infection in children.. Journal Name: Evidence-Based Nursing. Year: 2000	Review of a study [374] - no primary data
[375]	Authors: Turner T;. Title: Dipstick urinalysis for screening of childhood urinary tract infection. Journal Name: . Year: 2003	Describes itself as a systematic review, but is not. All relevant papers covered in our systematic review.

Reference ID	Bibliographic Information	Reason for rejecting study
[376]	Authors: Gorelick MH;Shaw KN;. Title: Screening tests for urinary tract infection in children: a meta-analysis. Journal Name: Pediatrics. Year: 1999	Covered by HTA
[377]	Authors: Kelly R;. Title: Identification of non-infected urine specimens in children. Journal Name: British Journal of Nursing. Year: 1995	Study in children attending a neuropathic bladder clinic
[378]	Authors: Berger RE;. Title: The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. Journal Name: Journal of Urology. Year: 2005 Sep	Commentary of a meta-analysis. Original meta-analysis included in guideline.
[379]	Authors: Chan RW;Chow KM;Tam LS;Li EK;Wong SM;Li PK;Szeto CC;. Title: Can the urine dipstick test reduce the need for microscopy for assessment of systemic lupus erythematosus disease activity?. Journal Name: Journal of Rheumatology. Year: 2005 May	In patients with systemic lupus erythematosus.
[380]	Authors: Lopez Vargas JA;Cuartas Trujillo MC;Molina Upegui OL;Restrepo Ceballos AC;Maya Carmona CY;Jaramillo VS;Donado Gomez JH;. Title: Usefulness of urinalysis and urine Gram stain in the diagnosis of urinary tract infection in hospitalized patients. Journal Name: Iatreia. Year: 2005	Foreign language
[381]	Authors: Nys S;van MT;Bartelds AIM;Stobberingh EE;. Title: Urinary tract infections in general practice patients: Diagnostic tests versus bacteriological culture. Journal Name: Journal of Antimicrobial Chemotherapy. Year: 2006	Study in adult women
[382]	Authors: Oregioni O;Delaunay P;Bruna P;Gaudart A;Lemichez E;Boquet P;Landraud L;. Title: Urinary interleukin-8 is elevated in urinary tract infections independently of the causative germs. Journal Name: Cytokine. Year: 2005	Laboratory based study - population unknown
[383]	Authors: Patel HD;Livsey SA;Swann RA;Bukhari SS;. Title: Can urine dipstick testing for urinary tract infection at point of care reduce laboratory workload?. Journal Name: Journal of Clinical Pathology. Year: 2005 Sep	Not in children.
[384]	Authors: Price CP;Newall RG;Boyd JC;. Title: Use of protein:creatinine ratio measurements on random urine samples for prediction of significant proteinuria: a systematic review. [51 refs]. Journal Name: Clinical Chemistry. Year: 2005 Sep	Majority of studies included patients with pre-eclampsia or renal disease
[385]	Authors: Richards D;Toop L;Chambers S;. Title: Treating negative dipstick dysuria decreases symptoms. Journal Name: Journal of Family Practice. Year: 2005	Synopsis only - Original trial evaluated response to antibiotics in adult women.
[386]	Authors: Wright OR;Safranek S;. Title: Urine dipstick for diagnosing urinary tract infection.. Journal Name: American Family Physician. Year: 2006 Jan 1	Non-systematic review

Antibiotic treatment

Reference ID	Bibliographic Information	Reason for rejecting study
[387]	Authors: Hari P;Mantan M;Bagga A;. Title: Management of urinary tract infections. Journal Name: Indian Journal of Pediatrics. Year: 2003	Commentary - not an RCT
[388]	Authors: . Title: Trimethoprim-sulfamethoxazole for treatment of urinary tract infections. Journal Name: Medical Letter on Drugs and Therapeutics. Year: 1975	Old paper - not within 20 years

Reference ID	Bibliographic Information	Reason for rejecting study
389	Authors: Adam D;Hager C;Dorn G;Bamberg P;. Title: A comparison of co-trimazine once daily and co-trimoxazole twice daily in treatment of urinary tract infections in children. Journal Name: Journal of Antimicrobial Chemotherapy. Year: 1982	Old paper - not within 20 years
390	Authors: Al Mugeiren MM;Qadri SMH;. Title: Bacteriologic profile and drug resistance in pediatric patients with symptomatic bacteriuria. Journal Name: Clinical Therapeutics. Year: 1996	Included in Cochrane review
391	Authors: Arav-Boger R;Leibovici L;Danon YL;. Title: Urinary tract infections with low and high colony counts in young women. Spontaneous remission and single-dose vs multiple-day treatment.. Journal Name: Archives of Internal Medicine. Year: 1994	Women over 18 years
392	Authors: Arrieta AC;Bradley JS;. Title: Empiric use of cefepime in the treatment of serious urinary tract infections in children.. Journal Name: Pediatric Infectious Disease Journal. Year: 2001	Neither cefepime nor ceftazidime are licenced for children in the UK
393	Authors: Bailey RR;Abbott GD;. Title: Treatment of urinary-tract infection with a single dose of amoxycillin. Journal Name: Nephron. Year: 1977	Old paper - not within 20 years
394	Authors: Bailey RR;. Title: What evidence is there for the use of single-dose therapy for urinary tract infections in children?. Journal Name: Infection. Year: 1994	Conference proceedings - not an RCT
395	Authors: Bailey RR;. Title: Single-dose/short-term therapy in children and in pregnant women. Journal Name: Infection. Year: 1994	Round table discussion document
396	Authors: Belet N;Islek I;Belet U;Sunter AT;Kucukoduk S;. Title: Comparison of trimethoprim-sulfamethoxazole, cephadroxil and cefprozil as prophylaxis for recurrent urinary tract infections in children. Journal Name: Journal of Chemotherapy. Year: 2004	Treatment of recurrent infection. Patients recruited from long-term residential care facility for the elderly.
397	Authors: Bergfors PG;. Title: Clinical studies on co-trimazine in children. Journal Name: Infection. Year: 1979	Co-trimazine not licensed in the UK
398	Authors: Bianchetti MG;Markus-Vecerova D;Schaad UB;. Title: Antibiotics in the treatment of urinary tract infections in hospitalized children. Journal Name: Schweizerische Medizinische Wochenschrift. Year: 1995	In hospitalised children
399	Authors: Bolding OT;. Title: Clinical comparison of cefadroxil, new oral cephalosporin, and cephalexin in uncomplicated urinary tract infection. Journal Name: Urology. Year: 1978	Old paper - not within 20 years
400	Authors: Bose W;Karama A;Linzenmeier G;Olbing H;Wellmann P;. Title: Controlled trial of co-trimoxazole in children with urinary-tract infection. Bacteriological efficacy and haematological toxicity. Journal Name: Lancet. Year: 1974	Old paper - not within 20 years
401	Authors: Bourillon A;Burgio GR;Steffens L;Kranz A;Noack M;Weippl G;Malaka-Zafiriu K;Gatzola M;Fall M;Tetanye E;Toporovski J;Araujo Vieralves LF;Kissling M;. Title: Cefetamet pivoxil in the treatment of acute urinary tract infections in children. Journal Name: Current Therapeutic Research, Clinical and Experimental. Year: 1994	Oral cefetamet Pivoxil not licenced for children in the UK
402	Authors: Brumfitt W;Hamilton-Miller JM;. Title: A review of the problem of urinary infection management and the evaluation of a potential new antibiotic.. Journal Name: Journal of Antimicrobial Chemotherapy. Year: 1984	Old paper - not within 20 years
403	Authors: Brumfitt W;Hamilton-Miller JM;. Title: Efficacy and safety profile of long-term nitrofurantoin in urinary infections: 18 years' experience. Journal Name: Journal of Antimicrobial Chemotherapy. Year: 1998	Patients ranged from 9-98 years. Data on children could not be extracted.

Reference ID	Bibliographic Information	Reason for rejecting study
[404]	Authors: Butler AV;Cullen MJ;Parry MO;Sylvester DG;Speller DC;. Title: Acute cystitis in young women. Treatment with citrated nalidixic acid compared with co-trimoxazole. Journal Name: Practitioner. Year: 1983	Study is in women 18-32 years
[405]	Authors: Cascio G;Pera A;. Title: [Cefazolin in treatment of acute urinary tract infections]. [Italian]. Journal Name: Clinica Terapeutica. Year: 1974	Old paper - not within 20 years
[406]	Authors: Casellas JM;Tome G;Exeni R;Grimoldi I;Goldberg M;Farinati AE;. Title: Serum and urinary cefpodoxime levels and time killing curves performed in the urine of children presenting urinary tract infections. Journal Name: Pathologie et Biologie. Year: 1993	Not about bacterial resistance patterns - not an RCT
[407]	Authors: Chrapowicki T;Krzyzanowska-Rogozinska T;Kurowska D;. Title: [Treatment of acute and chronic urinary tract infections in children with an urinary chemotherapeutic agent]. [German]. Journal Name: Zeitschrift fur Allgemeinmedizin. Year: 1975	Old paper - not within the last 20 years
[408]	Authors: Clemente E;Solli R;Mei V;Cera R;Caramia G;Carnelli V;Ruffini E;Venturoli V;Corsini A;. Title: Therapeutic efficacy and safety of pidotimod in the treatment of urinary tract infections in children. Journal Name: Arzneimittel-Forschung. Year: 1994	Pidotimod not licensed in the UK
[409]	Authors: Contopoulos-Ioannidis DG;Giotis ND;Baliatsa DV;Ioannidis JP;. Title: Extended-interval aminoglycoside administration for children: a meta-analysis.[see comment]. Journal Name: Pediatrics. Year: 2004	Review of aminoglycosides in paediatric infections, not UTI specific
[410]	Authors: Czerwionka-Szaflarska M;Pawlowska M;. Title: [Evaluation of the effectiveness of Uro-Vaxom in recurrent urinary tract infections in children]. [Polish]. Journal Name: Pediatria Polska. Year: 1996	Treatment of recurrent infections
[411]	Authors: Derluyn J;de Jaegher K;Vereecken R;Verduyn H;. Title: [Co-trimoxazole in urinary infections. Comparative double-blind study with an antibiotic]. [French]. Journal Name: Acta Urologica Belgica. Year: 1973	Old paper - not within 20 years
[412]	Authors: Ellerstein NS;Sullivan TD;Baliah T;Neter E;. Title: Trimethoprim/sulfamethoxazole and ampicillin in the treatment of acute urinary tract infections in children: a double-blind study. Journal Name: Pediatrics. Year: 1977	Old study - not within 20 years
[413]	Authors: Elo J;Ahava K;. Title: Cephalexin compared with ampicillin in urinary tract infections in children. Journal Name: Journal of Antimicrobial Chemotherapy. Year: 1975	Old paper - not within 20 years
[414]	Authors: Emoto Y;Higashima H;. Title: [Furadantin C for urinary tract infection]. [Japanese]. Journal Name: Hinyokika Kiyo - Acta Urologica Japonica. Year: 1971	Old paper - not within 20 years
[415]	Authors: Fanos V;Cataldi L;. Title: Cefixime in urinary tract infections with special reference to pediatrics: Overview. Journal Name: Journal of Chemotherapy. Year: 2001	Review article - not an RCT
[416]	Authors: Feldman W;Johnson DM;Newberry P;Weldon A;Naidoo S;. Title: Comparison of trimethoprim-sulfamethoxazole with sulfamethoxazole in urinary tract infections of children. Journal Name: Canadian Medical Association Journal. Year: 1975	Old paper - not within 20 years
[417]	Authors: Francois P;Croize J;Bost C;Wollschlager K;. Title: [Comparative study of cefixime versus amoxicillin-clavulanic acid combination in the oral treatment of urinary tract infections in children].[see comment]. [French]. Journal Name: Archives de Pediatrie. Year: 1995	Foreign Language

Reference ID	Bibliographic Information	Reason for rejecting study
418	Authors: Fujii R;Shinozaki T;Meguro H;Arimasu O;Izumi K;Osano M;Oikawa T;Shiro H;Sunakawa K;Iwata S;. Title: [Comparative, controlled study on an ampicillin suppository (KS-R 1) with an oral form of ampicillin in urinary tract infections]. [Japanese]. Journal Name: Japanese Journal of Antibiotics. Year: 1987	Foreign language paper
419	Authors: Ghiroa L;Craccoa AT;Sartora M;Comacchioa S;Zacchelloa G;Dall'Amicob R;. Title: Retrospective study of children with acute pyelonephritis: Evaluation of bacterial etiology, antimicrobial susceptibility, drug management and imaging studies. Journal Name: Nephron. Year: 2002	Not an RCT
420	Authors: Ginsburg CM;McCracken GH;Petruska M;. Title: Once-daily cefadroxil versus twice-daily cefaclor for treatment of acute urinary tract infections in children. Journal Name: Journal of Antimicrobial Chemotherapy. Year: 1982	Old paper - not within 20 years
421	Authors: Gonzalez E;Carranza C;Soto C;Romero P;. Title: [Comparative study of the activity of trimethoprim-sulfamethopyrazine and nitrofurantoin in urinary infections of children]. [Spanish]. Journal Name: Revista Chilena de Pediatria. Year: 1985	Foreign language paper
422	Authors: Hayashi I;Ijyuin M;. Title: [Clinical comparison of cephalexin and cephaloglycin in cystitis by double blind method]. [Japanese]. Journal Name: Hinyokika Kiyo - Acta Urologica Japonica. Year: 1970	Old paper - not within 20 years
423	Authors: Hellerstein S;. Title: Antibiotic treatment for urinary tract infections in pediatric patients. Journal Name: Minerva Pediatrica. Year: 2003	Commentary - not an RCT
424	Authors: Helwig H;Kohler M;Weigand W;. Title: [Treatment of urinary tract infections in childhood with Co-tetroxazin]. [German]. Journal Name: Zeitschrift fur Allgemeinmedizin. Year: 1983	Foreign language paper
425	Authors: Helwig H;. Title: Therapeutic strategies for urinary tract infections in children. Journal Name: Infection. Year: 1994	Commentary - not an RCT
426	Authors: Howard JE;Donoso E;Mimica I;Zilleruelo G;. Title: Gentamicin for urinary-tract infections in infants. Journal Name: Journal of Infectious Diseases. Year: 1971	Not sure if it is a RCT and >20 years old
427	Authors: Jodal U;. Title: The role of fosfomycin trometamol in the management of urinary tract infections in pediatrics.. Journal Name: Infection. Year: 1992	Commentary - not and RCT
428	Authors: Kamidono S;Ishigami J;Arakawa S;Umezu K;Ohmori H;Ishito N;Nihira H;Ishino T;Kurokawa K;Fujimura N;. Title: [Double-blind comparison of cefotetan and cefmetazole in complex urinary tract infections]. [Japanese]. Journal Name: Japanese Journal of Antibiotics. Year: 1983	Old paper - not within 20 years Foreign language paper
429	Authors: Kearns GL;Reed MD;Jacobs RF;Ardite M;Yogev RD;Blumer JL;. Title: Single-dose pharmacokinetics of ceftibuten (SCH 39720) in infants and children. Journal Name: Antimicrobial Agents and Chemotherapy. Year: 1991	Does not include UTI
430	Authors: Khan AJ;Kumar K;Evans HE;. Title: Single-dose gentamicin therapy of recurrent urinary tract infection in patients with normal urinary tracts. Journal Name: Journal of Pediatrics. Year: 1987	Not an RCT
431	Authors: Khan AJ;. Title: Efficacy of single-dose therapy of urinary tract infection in infants and children: a review. Journal Name: Journal of the National Medical Association. Year: 1994	Not a systematic review

Reference ID	Bibliographic Information	Reason for rejecting study
432	Authors: Krepler P;Steinbock H;. Title: [Clinical testing of a combination of sulfametrol and trimethoprim (Lidaprim) in urinary tract infections of children]. [German]. Journal Name: Wiener Medizinische Wochenschrift. Year: 1976	Old paper - not within the last 20 years
433	Authors: Kunin CM;. Title: Use of antimicrobial agents in treating urinary tract infection.. Journal Name: Advances in Nephrology From the Necker Hospital. Year: 1985	Commentary - not an RCT
434	Authors: Le Saux N;Pham B;Moher D;. Title: Evaluating the benefits of antimicrobial prophylaxis to prevent urinary tract infections in children: a systematic review.. Journal Name: CMAJ Canadian Medical Association Journal. Year: 2000	Antibiotics for prophylaxis rather than treatment.
435	Authors: Lewis G;. Title: Treatment of acute urinary tract infections with cefadroxil administered once daily. Journal Name: Journal of International Medical Research. Year: 1980	Old paper - not within 20 years
436	Authors: Lines DR;. Title: The effectiveness and safety of sulphamethoxazole-trimethoprim compound in childhood urinary infections. Journal Name: Australian Paediatric Journal. Year: 1973	Old study - not within the last 20 years
437	Authors: Malaka-Zafiriu K;Papadopoulos F;Avgoustidou-Savopoulou P;Papachristos F;. Title: Comparison of cefadroxil and ampicillin in the treatment of urinary tract infections in children. Journal Name: Clinical Therapeutics. Year: 1984	Old paper - not within 20 years
438	Authors: Mallo N;Dalet F;Hernandez J;. Title: [Clinical test of cefazedon (EMD 30 087) in complicated urinary infections (1)]. [Spanish]. Journal Name: Revista Clinica Espanola. Year: 1980	Old paper - not within 20 years
439	Authors: Mamzoridi K;Kasteridou N;Peonides A;Niopas I;. Title: Pharmacokinetics of cefixime in children with urinary tract infections after a single oral dose. Journal Name: Pharmacology and Toxicology. Year: 1996	Cohort of pharmacokinetics of cefixime in children - not an RCT, plus small sample size (n=6)
440	Authors: Martelli A;Cortecchia V;Ventriglia L;. Title: Aztreonam in the treatment of urinary tract infections: a multicenter trial. Journal Name: Chemotherapy. Year: 1989	Not an RCT
441	Authors: Mazzulli T;. Title: Resistance trends in urinary tract pathogens and impact on management.. Journal Name: Journal of Urology. Year: 2002	Not antibiotic treatment - narrative review on resistance trends in all age groups.
442	Authors: Minkov N;Zlatanov Z;Zozikov E;Staneva D;Krusheva R;. Title: [Brulamycin in the treatment of urinary infections--microbiological and clinical research]. [Bulgarian]. Journal Name: Vutreshni Bolesti. Year: 1984	Old paper - not within the last 20 years Foreign language paper
443	Authors: Moe OJ;Meberg A;Eng J;. Title: Ampicillin and pivampicillin in the treatment of urinary tract infection in children. Journal Name: Scandinavian Journal of Infectious Diseases. Year: 1977	Old paper - not within 20 years
444	Authors: Naber K;Kaldewey W;. Title: [Comparative study of cefaclor versus amoxicillin in urinary tract infections]. [German]. Journal Name: Infection. Year: 1979	Old paper - not within the last 20 years Foreign language paper
445	Authors: Nicolle LE;. Title: Asymptomatic bacteriuria: when to screen and when to treat. Journal Name: Infectious Disease Clinics of North America. Year: 2003	Commentary on asymptomatic bacteruria
446	Authors: Olbing H;Neussel H;Senge T;Hagel K;Linzenmeier G;. Title: [Problems in the therapy of pseudomonas infections of the urinary tract. Alternating comparison of carbenicillin and gentamycin in children]. [German]. Journal Name: Deutsche Medizinische Wochenschrift. Year: 1971	Old paper - not within the last 20 years Foreign language paper

Reference ID	Bibliographic Information	Reason for rejecting study
447	Authors: Palcoux JB;Raynaud EJ;Borderon JC;Dalous A;Geisert J;Pennaforte F;Peyramond D;Peyrille F;. Title: [Clinical trial of a clavulanic acid-amoxicillin combination in urinary infections in children]. [French]. Journal Name: Annales de Pediatrie. Year: 1986	Half of the patients had an anomoly of the urinary collecting system
448	Authors: Petersen KE;Nielsen EL;Vejlsgaard R;. Title: [Bacteriuria developing in children during treatment with ampicillin and pivampicillin]. [Danish]. Journal Name: Ugeskrift for Laeger. Year: 1977	Old paper - not within 20 years Foreign language
449	Authors: Piekkala P;Huovinen P;Valimaki I;. Title: Comparative study of cefuroxime vs. amoxycillin in the parenteral treatment of children with upper urinary tract infection. Journal Name: Current Therapeutic Research, Clinical and Experimental. Year: 1985	Commentary - not an RCT
450	Authors: Plumridge RJ;Golledge CL;. Title: Treatment of urinary tract infection. Clinical and economic considerations. Journal Name: Pharmacoeconomics. Year: 1996	Commentary - not an RCT
451	Authors: Ponticelli C;Zucchelli P;Casucci G;Cervellati I;Dalla RC;Giro C;Motolese M;. Title: Multicentre comparison of cephacetrile and ampicillin in the treatment of urinary tract infections. Journal Name: European Journal of Clinical Pharmacology. Year: 1974	Old paper - not within 20 years
452	Authors: Price JD;Harding JW;. Title: The use of amoxycillin in treatment of urinary tract infection in general practice. Journal Name: British Journal of Clinical Practice. Year: 1973	Old paper - not within 20 years
453	Authors: Principi N;Corda R;Bassetti D;Varese LA;Peratoner L;. Title: Fosfomycin trometamol versus netilmicin in children's lower urinary tract infections. Journal Name: Chemotherapy. Year: 1990	Fosfomycin Trometamol not licensed in the UK
454	Authors: Pylkkanen J;Vilska J;Koskimies O;. Title: The length of antimicrobial therapy in upper vs. lower urinary tract infection of childhood. Journal Name: Acta Paediatrica Scandinavica. Year: 1981	Included in Cochrane review (Ref ID 87) but sulfafurazole not licenced for children in the UK
455	Authors: Reed K;Newton W;. Title: Oral or IV antibiotics for the treatment of febrile children with UTIs?. Journal Name: Journal of Family Practice. Year: 1999	Short summary only - full text report of study available (Ref ID 153)
456	Authors: Reid G;Bruce AW;Cook RL;Llano M;. Title: Effect on urogenital flora of antibiotic therapy for urinary tract infection. Journal Name: Scandinavian Journal of Infectious Diseases. Year: 1990	Study in women aged 18-72 years
457	Authors: Rodriguez W;Delucchi C;Bidegain MA;Rodriguez MS;Gleisner A;Figueroa S;. Title: [Treatment of urinary tract infections in children with trimethoprim-sulfamethoxypyridazine]. [Spanish]. Journal Name: Revista Chilena de Pediatria. Year: 1983	Old paper - not within 20 years Foreign language
458	Authors: Rubin RH;Shapiro ED;Andriole VT;Davis RJ;Stamm WE;. Title: Evaluation of new anti-infective drugs for the treatment of urinary tract infection. Infectious Diseases Society of America and the Food and Drug Administration. Journal Name: Clinical Infectious Diseases. Year: 1992	Genral guidelines for UTI drugs - not children specific
459	Authors: Rushton HG;. Title: Urinary tract infections in children: Epidemiology, evaluation, and management. Journal Name: Pediatric Clinics of North America. Year: 1997	Book chapter - not an RCT
460	Authors: Sadanobu K;Shoji T;Nishimura Y;Miyazaki S;. Title: [Effect of combination therapy with TSP tablet and antibiotics for acute cystitis]. [Japanese]. Journal Name: Hinyokika Kiyo - Acta Urologica Japonica. Year: 1967	Old paper - not within 20 years Foreign language

Reference ID	Bibliographic Information	Reason for rejecting study
[461]	Authors: Schach H;Scheidt J;Neussel H;. Title: [Results of treatment with trimethoprim-sulfamethoxazole in nonspecific urinary tract infections in pediatric urology]. [German]. Journal Name: Monatsschrift fur Kinderheilkunde. Year: 1972	Old paper - not within the lst 20 years
[462]	Authors: Shapiro ED;. Title: Short course antimicrobial treatment of urinary tract infections in children: a critical analysis. Journal Name: Pediatric Infectious Disease. Year: 1982	Old paper - not within 20 years
[463]	Authors: Stansfeld JM;. Title: Duration of treatment for urinary tract infections in children. Journal Name: British Medical Journal. Year: 1975	Outcome is reinfection, but compares two week treatment with 6 month prophylaxis.
[464]	Authors: Stein GE;. Title: Fosfomycin tromethamine: single-dose treatment of acute cystitis.. Journal Name: International Journal of Fertility and Womens Medicine. Year: 1999	Trials in adult women. Children's data was not available although narrative was included.
[465]	Authors: Tynan AP;Macis FR;Ward-McQuaid JN;. Title: Nifuratel in urinary infections. Journal Name: British Journal of Urology. Year: 1969	Old paper - not within 20 years
[466]	Authors: Uijtendaal EV;Rademaker CM;Schobben AF;Fleer A;Kramer WL;van Vught AJ;Kimpen JL;van Dijk A;. Title: Once-daily versus multiple-daily gentamicin in infants and children. Journal Name: Therapeutic Drug Monitoring. Year: 2001	Not only UTI
[467]	Authors: Varde AB;Shetty HG;Jadav SK;Sheth SM;Acharya VN;Satoskar RS;. Title: Comparison of trimethoprim in combination with sulfadiazine or sulfamethoxazole in the treatment of urinary tract infections. Journal Name: Journal of Postgraduate Medicine. Year: 1981	Old paper - not within 20 years
[468]	Authors: Vlatkovic G;Babic I;. Title: [Treatment of urinary tract infection in the child using Ceporex (cephalexin)]. [Croatian]. Journal Name: Lijecnicki Vjesnik. Year: 1972	Old paper - not within 20 years Foreign language
[469]	Authors: Weber HP;Aberfeld U;Hildenbrand G;Knopfle G;. Title: [Treatment of initial urinary tract infection in children with cotrifamole and cotrimoxazole. A double-blind study]. [German]. Journal Name: Deutsche Medizinische Wochenschrift. Year: 1982	Old paper - not within 20 years
[470]	Authors: Whitworth JA;. Title: Single-dose therapy in the management of urinary tract infections.. Journal Name: Medical Journal of Australia. Year: 1986	Not an RCT
[471]	Authors: Yoshida K;Uchijima Y;Kobayashi N;Suwata J;Nakame Y;Saitoh H;Negishi T;Yamada T;Kageyama Y;Kura N;. Title: [Clinical efficacy of aztreonam in patients with complicated urinary tract infections]. [Japanese]. Journal Name: Hinyokika Kiyo - Acta Urologica Japonica. Year: 1988	Foreign Language paper
[472]	Authors: Pohl A;Antes G;Forster J;. Title: Modes of administration of antibiotics for symptomatic urinary tract infections. Journal Name: The Cochrane Library. Year: 2005	Cochrane protocol only
[473]	Authors: Kahan NR;Chinitz DP;Kahan E;. Title: Longer than recommended empiric antibiotic treatment of urinary tract infection in women: an avoidable waste of money. Journal Name: Journal of Clinical Pharmacy and Therapeutics. Year: 2004 Feb	Economic recommendations
[474]	Authors: McKinnon PS;Neuhauser MM;. Title: Efficacy and cost of ampicillin-sulbactam and ticarcillin-clavulanate in the treatment of hospitalized patients with bacterial infections. Journal Name: Pharmacotherapy. Year: 1999 Jun	Not UTI specific

Reference ID	Bibliographic Information	Reason for rejecting study
475	Authors: Wang EC;Grasela TH;Walawander CA;. Title: Applying epidemiology-based outcomes research to clinical decision-making. A hypothetical model of biotechnology therapy in gram-negative sepsis. Journal Name: Pharmacoeconomics. Year: 1999 Apr	Not UTI specific
476	Authors: Przybylski KG;Rybak MJ;Martin PR;Weingarten CM;Zaran FK;Stevenson JG;Levine DP;. Title: A pharmacist-initiated program of intravenous to oral antibiotic conversion. Journal Name: Pharmacotherapy. Year: 1997 Mar	Unable to extract UTI information from other infections and childrens data from adult data
477	Authors: Adelman RD;Halsted CC;Jordan GW;Russo J;. Title: Use of urinary enzyme activities in the early detection of aminoglycoside nephrotoxicity: a study in children and adults receiving gentamicin or netilmicin. Journal Name: Proceedings of the Western Pharmacology Society. Year: 1981	Old paper - not within 20 years
478	Authors: Carlsen NL;Hesselbjerg U;Glenting P;. Title: Comparison of long-term, low-dose pivmecillinam and nitrofurantoin in the control of recurrent urinary tract infection in children. An open, randomized, cross-over study. Journal Name: Journal of Antimicrobial Chemotherapy. Year: 1985 Oct	Treatment for children with vesicoureteric reflux and current UTI
479	Authors: Demos CH;Green E;. Title: Review of clinical experience with amdinocillin monotherapy and comparative studies. [Review] [27 refs]. Journal Name: American Journal of Medicine. Year: 1983 Aug 29	Old paper - not within last 20 years
480	Authors: Itsarayoungyuen S;Riff L;Schauf V;Hamilton L;Otrembiak J;Vidyasagar D;. Title: Tobramycin and gentamicin are equally safe for neonates: results of a double-blind randomized trial with quantitative assessment of renal function. Journal Name: Pediatric Pharmacology. Year: 1982	Unable to extract data for UTI from other bacterial infections
481	Authors: . Title: The management of urinary tract infection in children. [Review] [43 refs]. Journal Name: Drug and Therapeutics Bulletin. Year: 1997 Sep	Commentary - not an RCT
482	Authors: Hoppu K;Koskimies O;Vilska J;. Title: Trimethoprim in the treatment of acute urinary tract infections in children. Journal Name: International Journal of Clinical Pharmacology, Therapy, and Toxicology. Year: 1988 Feb	Sulfisoxazole not licenced in the UK
483	Authors: Khan AJ;Kumar K;Evans HE;. Title: Three-day antimicrobial therapy of urinary tract infection. Journal Name: Journal of Pediatrics. Year: 1981 Dec	Old paper - not within 20 years
484	Authors: Alban J;. Title: Urinary tract infections in children: experience with nalidixic acid. Journal Name: Current Therapeutic Research, Clinical and Experimental. Year: 1970 Sep	Old paper - not within 20 years
485	Authors: Sanders WE;. Title: Ceftriaxone in treatment of serious infections. Urinary tract infections.. Journal Name: Hospital Practice (Office Edition). Year: 1991 Sep	Commentary - not an RCT
486	Authors: Martin AJ;Lacey RW;. Title: A blind comparison of the efficacy and incidence of unwanted effects of trimethoprim and co-trimoxazole in the treatment of acute infection of the urinary tract in general practice. Journal Name: British Journal of Clinical Practice. Year: 1999	Study mainly in adults - cannot extract data on children
487	Authors: Gauthier M;Chevalier I;Sterescu A;Bergeron S;Brunet S;Taddeo D;. Title: Treatment of urinary tract infections among febrile young children with daily intravenous antibiotic therapy at a day treatment center. Journal Name: Pediatrics. Year: 2004	Cohort study - not an RCT

Reference ID	Bibliographic Information	Reason for rejecting study
[488]	Authors: Michael M;Hodson EM;Craig JC;Martin S;Moyer VA;. Title: Short compared with standard duration of antibiotic treatment for urinary tract infection: a systematic review of randomised controlled trials. Journal Name: Archives of Disease in Childhood. Year: 2002	Re-print of cochrane review.
[489]	Authors: Chao SM;Chong CY;Tan-Hendrick A;Tan ASL;Ng WYM;. Title: Efficacy and safety of once-a-day gentamicin in the treatment of childhood acute pyelonephritis. Journal Name: Pediatric Nephrology. Year: 2001	Study published as full article in REF ID 125
[490]	Authors: Michael M;Hodson E;Craig J;Martin S;Moyer V;. Title: Short versus standard duration antibiotic therapy for urinary tract infection in children: a meta-analysis.Supplement. Journal Name: Pediatric Nephrology. Year: 2001	Abstract only - Inflammatory reaction and leukocyte trafficking, not antibiotic treatment
[491]	Authors: Carapetis J;Jaquiery A;Buttery J;Starr M;. Title: A randomised controlled trial of once-daily gentamicin in children with urinary tract infections.. Journal Name: Australian and New Zealand Journal of Medicine. Year: 1999	Abstract only - have the full text (Ref ID 122)
[492]	Authors: Centre for Reviews and Dissemination.;. Title: Short-course versus conventional length antimicrobial therapy for uncomplicated lower urinary tract infections in children: a meta-analysis of 1279 patients (Structured abstract). Journal Name: The Cochrane Library. Year: 2005	Summary comments from Centre for reviews and disemmination
[493]	Authors: Centre for Reviews and Dissemination.;. Title: A meta-analysis of randomized, controlled trials comparing short- and long-course antibiotic therapy for urinary tract infections in children (Structured abstract). Journal Name: The Cochrane Library. Year: 2005	From database of Abstracts of reviews of effects - reviews a meta-analysis.
[25]	Authors: Coulthard MG;Vernon SJ;Lambert HJ;Matthews JNS;. Title: A nurse led education and direct access service for the management of urinary tract infections in children: Prospective controlled trial. Journal Name: British Medical Journal. Year: 2003	Outcomes not antibiotic treatment related. Include rate and quality of diagnosis, prophylaxis and prevention of scarring.
[494]	Authors: Tong X;Wang E;Feng L;. Title: Clinical study of oral cefixime in the treatment of urinary tract infection in 35 children. Journal Name: Chinese Journal of Antibiotics. Year: 2005	Foreign language
[495]	Authors: Dromigny JA;Nabeth P;Juergens-Behr A;Perrier-Gros-Claude JD;. Title: Risk factors for antibiotic-resistant Escherichia coli isolated from community-acquired urinary tract infections in Dakar, Senegal. Journal Name: Journal of Antimicrobial Chemotherapy. Year: 2005 Jul	Antibiotic resistance in Senegal is unlikely to apply to the UK context.
[496]	Authors: Lutter SA;Currie ML;Mitz LB;Greenbaum LA;. Title: Antibiotic resistance patterns in children hospitalized for urinary tract infections.. Journal Name: Archives of Pediatrics & Adolescent Medicine. Year: 2005 Oct	Study about resistance patterns in Milwaukee, USA. Unlikely to apply to the UK context.

Symptomatic treatment

Reference ID	Bibliographic Information	Reason for rejecting study
[497]	Authors: Rogers J;. Title: Pass the cranberry juice... herbal remedy for the treatment of urinary tract infections. Journal Name: Nursing Times. Year:	Opinion paper only

Reference ID	Bibliographic Information	Reason for rejecting study
498	Authors: Miller JL;Krieger JN;. Title: Urinary tract infections cranberry juice, underwear, and probiotics in the 21st century. [Review] [31 refs]. Journal Name: Urologic Clinics of North America. Year: 2002 Aug	Opinion paper only. Not a systematic review and based on poor quality primary studies. In adults, not children
499	Authors: Lynch DM;. Title: Cranberry for prevention of urinary tract infections.. Journal Name: American Family Physician. Year: 2004 Dec 1	Included in cochrane review
500	Authors: Lowe FC;Fagelman E;. Title: Cranberry juice and urinary tract infections: what is the evidence?. [Review] [22 refs]. Journal Name: Urology. Year: 2001 Mar	Review but no quality assessment of included studies. No RCTs.
501	Authors: Kiel RJ;Nashelsky J;Robbins B;Bondi S;. Title: Clinical inquiries. Does cranberry juice prevent or treat urinary tract infection?. [Review] [6 refs]. Journal Name: Journal of Family Practice. Year: 2003 Feb	Letter only
502	Authors: Hrastinger A;Dietz B;Bauer R;Sagraves R;Mahady G;. Title: Is there clinical evidence supporting the use of botanical dietary supplements in children?. Journal Name: Journal of Pediatrics. Year: 2005	Not UTI specific
503	Authors: Greenberg JA;Newman SJ;Morgan MA;. Title: Cranberries and urinary-tract health: a knowledge assessment of American College of Obstetricians and Gynecologists fellows. Journal Name: Journal of Alternative and Complementary Medicine. Year:	Letter only
504	Authors: Berger RE;. Title: Cranberries for preventing urinary tract infections. Journal Name: Journal of Urology. Year: 2005 Jun	Abstract of cochrance review
505	Authors: . Title: Cranberry and urinary tract infection.. Journal Name: Drug and Therapeutics Bulletin. Year: 2005 Mar	Non-systematic review covering three groups, adult women, children with neuropathic bladder and older men and women.
506	Authors: Avorn J;Monane M;Gurwitz JH;Glynn RJ;Choodnovskiy I;Lipsitz LA;. Title: Reduction of bacteriuria and pyuria after ingestion of cranberry juice. Journal Name: JAMA. Year: 1994 Mar	Previous UTI was significantly different between the groups at 6 months (7% of cranberry group vs. 25% of placebo group) and at 12 months (17% of cranberry group vs. 33% of placebo group). Suggests non-randomisation.
507	Authors: Abu Daia JM;Al Aaly MA;De Castro R;. Title: Urinary tract infection in childhood. A practical approach and pediatric urologists point of view. [Review] [15 refs]. Journal Name: Saudi Medical Journal. Year: 2000 Aug	Review only - no primary data and not well referenced.
508	Authors: Baraff LJ;. Title: Management of fever without source in infants and children. [Review] [121 refs]. Journal Name: Annals of Emergency Medicine. Year: 2000 Dec	Review only - no primary data
509	Authors: Avner JR;Baker MD;. Title: Management of fever in infants and children. [Review] [64 refs]. Journal Name: Emergency Medicine Clinics of North America. Year: 2002 Feb	Review only - no primary data
510	Authors: Miser WF;. Title: Fever without source in infants and young children--a hot potato?[comment]. Journal Name: American Family Physician. Year: 2001 Oct 1	not RCT or SR
511	Authors: Neveus T;Lackgren G;Tuvemo T;Hetta J;Hjalmas K;Stenberg A;. Title: Enuresis--background and treatment. [Review] [561 refs]. Journal Name: Scandinavian Journal of Urology and Nephrology Supplementum. Year: 2000	Review only - no primary data
512	Authors: Shaw KN;Gorelick MH;. Title: Urinary tract infection in the pediatric patient. [Review] [88 refs]. Journal Name: Pediatric Clinics of North America. Year: 1999	Review only - no primary data

Reference ID	Bibliographic Information	Reason for rejecting study
513	Authors: Bachur R;. Title: Nonresponders: prolonged fever among infants with urinary tract infections. Journal Name: Pediatrics. Year: 2000 May	Not related to symptomatic treatment
514	Authors: Roberts JA;. Title: Management of pyelonephritis and upper urinary tract infections. [Review] [57 refs]. Journal Name: Urologic Clinics of North America. Year: 1999 Nov	Review only - no primary data
515	Authors: Strong S;. Title: Effective treatment for children's enuresis. Journal Name: Nursing Times. Year: 1998 Jan 7	Opinion paper - no primary data and not UTI specific
516	Authors: . Title: No evidence for practice of alternating doses of paracetamol and ibuprofen in children with fever. Journal Name: Pharmaceutical Journal. Year:	not RCT or SR
517	Authors: Shortliffe LM;. Title: The management of urinary tract infections in children without urinary tract abnormalities. [Review] [52 refs]. Journal Name: Urologic Clinics of North America. Year: 1995 Feb	Review only - no primary data
518	Authors: Dagan R;Sofer S;Philip M;Shachak E;. Title: Ambulatory care of febrile infants younger than 2 months of age classified as being at low risk for having serious bacterial infections. Journal Name: Journal of Pediatrics. Year: 1988	In children with normal urinalysis Children with serious bacterial infections - not UTI specific.
519	Authors: Yurdakok M;Kinik E;Beduk Y;. Title: Treatment of enuresis: A study with imipramine, amitriptyline, chlordiazepoxide-clidinium and piracetam. Journal Name: Turkish Journal of Pediatrics. Year: 1986	Not UTI specific
520	Authors: Durbin Jr WA;Peter G;. Title: Management of urinary tract infections in infants and children. Journal Name: Pediatric Infectious Disease. Year: 1984	Review only - no primary data
521	Authors: Scharer K;Manz F;. Title: Renal handling of citrate in children with various kidney disorders. Journal Name: International Journal of Pediatric Nephrology. Year: 1985	Not related to symptomatic treatment
522	Authors: Shimoyama A;. Title: On enuresis of adolescents. Journal Name: Japanese Journal of Psychosomatic Medicine. Year: 1985	Foreign language
523	Authors: Lynch NT;Grunert BK;Vasudevan SV;Severson RA;. Title: Enuresis: Comparison of two treatments. Journal Name: Archives of Physical Medicine and Rehabilitation. Year: 1984	Not UTI specific
524	Authors: Louis JJ;. Title: Non steroidal anti-inflammatory drugs in pediatrics. Journal Name: Pediatrie. Year: 1984	Wrong topic
525	Authors: Mehrotra SN;Liu L;Srivastava JR;Singh SB;. Title: Evaluation of various methods in treatment of enuresis. Journal Name: Indian Pediatrics. Year: 1980	No indication whether patients had UTI
526	Authors: Reid G;Devillard E;. Title: Probiotics for mother and child. [Review] [95 refs]. Journal Name: Journal of Clinical Gastroenterology. Year: 2004 Jul	Review only - no primary data
527	Authors: Rogers J;. Title: An overview of the management of nocturnal enuresis in children. [Review] [55 refs]. Journal Name: British Journal of Nursing. Year: 2003 Aug 14	not RCT or SR
528	Authors: Yeung CK;. Title: Nocturnal enuresis (bedwetting). [Review] [41 refs]. Journal Name: Current Opinion in Urology. Year: 2003 Jul	Review only - no primary data
529	Authors: Rushton HG;. Title: Evaluation of the enuretic child. [Review] [38 refs]. Journal Name: Clinical Pediatrics. Year: 1993 Jul	Review only - no primary data

Reference ID	Bibliographic Information	Reason for rejecting study
[530]	Authors: Warady BA;Alon U;Hellerstein S;. Title: Primary nocturnal enuresis: current concepts about an old problem. [Review] [20 refs]. Journal Name: Pediatric Annals. Year: 254 May	Review only - no primary data
[531]	Authors: Rushton HG;. Title: Nocturnal enuresis: epidemiology, evaluation, and currently available treatment options. [Review] [44 refs]. Journal Name: Journal of Pediatrics. Year: 1989 Apr	Review - no primary data. Poorly referenced.
[532]	Authors: Lovering JS;Tallett SE;McKendry JB;. Title: Oxybutynin efficacy in the treatment of primary enuresis. Journal Name: Pediatrics. Year: 1988 Jul	In children with no UTI and no history of UTI
[533]	Authors: Swedish Collaborative Study Group.;. Title: Nalidixic acid plus sodium citrate twice daily in treatment of acute urinary tract infection. Journal Name: Scandinavian Journal of Primary Health Care. Year: 1988	In women >16
[534]	Authors: Ferry S;Burman LG;Widberg B;Calmenius C;. Title: Short-term nalidixic acid plus sodium citrate in acute lower urinary tract infection. Journal Name: Scandinavian Journal of Infectious Diseases. Year: 1987	Women 19-31 years
[535]	Authors: Elinder G;Soback S;. Title: Effect of Uristop on primary nocturnal enuresis. A prospective randomized double-blind study. Journal Name: Acta Paediatrica Scandinavica. Year: 1985 Jul	In psychiatric population - no UTI
[536]	Authors: Spooner JB;. Title: Alkalinisation in the management of cystitis. Journal Name: Journal of International Medical Research. Year: 1984	In women aged 18-60
[537]	Authors: Winterborn MH;. Title: The management of urinary infections in children. Journal Name: British Journal of Hospital Medicine. Year: 458 Sep	Review only - no primary data
[538]	Authors: Stewart MA;. Title: Treatment of bedwetting. Journal Name: JAMA. Year: 1975 Apr 21	Opinion paper only - no primary data
[539]	Authors: Aperia A;Berg U;Broberger O;. Title: Renal bicarbonate reabsorption and hydrogen ion excretion in children with recurrent urinary tract infections. The effect of fluorohydrocortisone. Journal Name: Acta Paediatrica Scandinavica. Year: 1974 Mar	In children with recurrent UTI
[540]	Authors: Johnstone JM;. Title: Cystometry and evaluation of anticholinergic drugs in enuretic children. Journal Name: Journal of Pediatric Surgery. Year: 1972 Feb	Enuresis due to psychological stress - not UTI
[541]	Authors: Murphy S;Nickols J;Umphress A;Hammar S;Eddy R;Chapman W;. Title: Adolescent enuresis. A multiple contingency hypothesis. Journal Name: JAMA. Year: 1971 Nov 22	UTI not mentioned and population of malnourished children
[542]	Authors: . Title: Sedative and stimulant compared in enuresis. Journal Name: Practitioner. Year: 1970 Apr	Not UTI specific
[543]	Authors: Esperanca M;Gerrard JW;. Title: Nocturnal enuresis: comparison of the effect of imipramine and dietary restriction on bladder capacity. Journal Name: Canadian Medical Association Journal. Year: 1969 Dec 13	Only in children with sterile urine
[544]	Authors: Miyao M;Hasegawa Y;Matsuda H;Matsumura I;Imaoka M;. Title: Urinary alkaline phosphatase level in children. Journal Name: Tokushima Journal of Experimental Medicine. Year: 1968 May	Not UTI specific
[545]	Authors: Agarwal HC;Mohan D;Mukerji DP;. Title: Eneuresis. An etiological and therapeutic review. [Review] [38 refs]. Journal Name: Indian Journal of Medical Sciences. Year: 1967 Oct	Review - no primary data

Reference ID	Bibliographic Information	Reason for rejecting study
546	Authors: Akpede GO;Akenzua GI;. Title: Management of children with prolonged fever of unknown origin and difficulties in the management of fever of unknown origin in children in developing countries. Journal Name: Paediatric Drugs. Year: 2001	Review only - no primary data
547	Authors: Akpede GO;Akenzua GI;. Title: Aetiology and management of children with acute fever of unknown origin. Journal Name: Paediatric Drugs. Year: 2001	Review only - no primary data
548	Authors: Aneja S;. Title: Nocturnal enuresis. Journal Name: Indian Journal of Pediatrics. Year: 2002 Aug	Review paper - no primary data
549	Authors: Ashouri N;Butler J;Vargas-Shiraishi OM;Singh J;Arrieta A;. Title: Urinary tract infection in neonates: How aggressive a workup and therapy?. Journal Name: Infections in Medicine. Year:	Management plan - not related to symptomatic treatment
550	Authors: Bernard-Bonnin AC;. Title: Diurnal enuresis in childhood. [Review] [26 refs]. Journal Name: Canadian Family Physician. Year: 2000 May	Not UTI specific
551	Authors: Meremikwu M;Oyo-Ita A;. Title: Paracetamol for treating fever in children. Journal Name: The Cochrane Library. Year: 2005	Not specifically children with UTI
552	Authors: Glazener CMA;Evans JHC;. Title: Desmopressin for nocturnal enuresis in children. Journal Name: The Cochrane Library. Year: 2005	Not children with suspected UTI
553	Authors: Glazener CMA;Evans JHC;Cheuk DKL;. Title: Complementary and miscellaneous interventions for nocturnal enuresis in children. Journal Name: The Cochrane Library. Year: 2005	not children with suspected UTI
554	Authors: Centre for Reviews and Dissemination.;. Title: Treating fever in children: paracetamol or ibuprofen? (Structured abstract). Journal Name: The Cochrane Library. Year: 2005	not specifically children with UTI
555	Authors: El Radhi AS;Board C;. Title: Providing adequate treatment for children with nocturnal enuresis. Journal Name: British Journal of Community Nursing. Year:	not a RCT, not children with UTI
556	Authors: Cichocka E;Majchrzyk-Ossowska T;Frelek M;. Title: Complications of desmopressin administration in nocturnal enuresis in children. Journal Name: Pediatria Polska. Year: 1996	Foreign language
557	Authors: Floret D;. Title: Acute fever in children. Criteria to identify serious illness in febrile children. Journal Name: Revue du Praticien. Year:	Foreign language
558	Authors: Hagglund TB;. Title: Enuretic children treated with fluid restriction or forced drinking. A clinical and cystometric study. Journal Name: Annales Paediatriae Fenniae. Year: 1965	Not UTI specific
559	Authors: Kellner JD;. Title: Management of fever without source in children: Changing times. Journal Name: Paediatrics and Child Health. Year: 2003	Not specifically children with out UTI
560	Authors: Malhotra SM;Kennedy II WA;. Title: Urinary tract infections in children: Treatment. Journal Name: Urologic Clinics of North America. Year: 2004	Review only - no primary data
561	Authors: Marchetti F;Bua J;Maschio M;Barbi E;. Title: Symptomatic treatment of fever and pain in paediatric practice. Journal Name: Medico e Bambino. Year:	Foreign language
562	Authors: McCarthy PL;Klig JE;Kennedy WP;Kahn JS;. Title: Fever without apparent source on clinical examination, lower respiratory infections in children, and enterovirus infections. Journal Name: Current Opinion in Pediatrics. Year: 2000	Review only - no primary data

Reference ID	Bibliographic Information	Reason for rejecting study
563	Authors: McCarthy PL;. Title: Fever without apparent source on clinical examination. Journal Name: Current Opinion in Pediatrics. Year: 2002	Review only - no primary data
564	Authors: Nappo S;Del Gado R;Chiozza ML;Biraghi M;Ferrara P;Caione P;. Title: Nocturnal enuresis in the adolescent: A neglected problem. Journal Name: BJU International. Year: 2002	Not an RCT
565	Authors: Nelson DS;Gurr MB;Schunk JE;. Title: Management of febrile children with urinary tract infections. Journal Name: American Journal of Emergency Medicine. Year:	Not related to UTI epidemiology
566	Authors: Tobias JD;. Title: Weak analgesics and nonsteroidal anti-inflammatory agents in the management of children with acute pain. [Review] [36 refs]. Journal Name: Pediatric Clinics of North America. Year: 2000 Jun	Review only - no primary data
567	Authors: Wille S;. Title: Primary nocturnal enuresis in children. Background and treatment. Journal Name: Scandinavian Journal of Urology and Nephrology Supplementum. Year: 1994	Review only - no primary data
568	Authors: Yannakoyorgos K;Ioannides E;Zahariou A;Anagnostopoulos D;Kasselas V;Kalinderis A;. Title: Management of nocturnal enuresis in children with desmopressin and bladder physiotherapy. Journal Name: Pediatric Surgery International. Year: 1998 Apr	Not UTI specific
569	Authors: Norgaard JP;Van Gool JD;Hjalmas K;Djurhuus JC;Hellstrom A;. Title: Standardization and definitions in lower urinary tract dysfunction in children. Journal Name: British Journal of Urology. Year: 1998	Enuresis and urinary incontinence - not UTI specific
570	Authors: De Grazia E;Cimador M;. Title: Combined oxybutinin-desmopressin therapy in the treatment of nocturnal enuresis with urinary disorders. Journal Name: Minerva Pediatrica. Year: 1999	Foreign language
571	Authors: Dairiki Shortliffe LM;McCue JD;. Title: Urinary tract infection at the age extremes: Pediatrics and geriatrics. Journal Name: American Journal of Medicine. Year: 2002	Review only - no primary data
572	Authors: Caione P;Arena F;Biraghi H;Cigna RM;Chendi D;Chiozza ML;De Lisa A;De Grazia E;Fano M;Formica P;Garofalo S;Gramenzi R;Von Heland M;Lanza P;Lanza T;Maff. Title: Nocturnal enuresis and daytime wetting: A multicentric trial with oxybutynin and desmopressin. Journal Name: European Urology. Year: 1997	Onlu in children with no UTI
573	Authors: McCarthy PL;Bachman DT;Shapiro ED;Baron MA;. Title: Fever without apparent source on clinical examination, lower respiratory infections in children, bacterial infections, and acute gastroenteritis and diarrhea of infancy and early childhood. Journal Name: Current Opinion in Pediatrics. Year: 1995	Text book chapter - no primary data
574	Authors: Van DV;Van d;Suijlekom-Smit LWA;. Title: Acute infections in children. Journal Name: Geneesmiddelenbulletin. Year: 1992	Foreign language
575	Authors: Di MP;Agniel R;Gaillard JL;Denys P;. Title: Effects of cranberry juice on uropathogenic Escherichia coli in vitro biofilm formation. Journal Name: Journal of Chemotherapy. Year: 2005 Oct	Non-systematic review
576	Authors: Howell AB;Reed JD;Krueger CG;Winterbottom R;Cunningham DG;Leahy M;. Title: A-type cranberry proanthocyanidins and uropathogenic bacterial anti-adhesion activity. Journal Name: Phytochemistry. Year: 2005 Sep	Study of anti-adhesion activity in human urine
577	Authors: Najm W;. Title: Antimicrobial activity of urine ater ingestion of cranberry. Journal Name: Focus on Alternative and Complementary Therapies. Year: 2005	Study of antimicrobial activity in adults without UTI

Predictors of recurrence

Reference ID	Bibliographic Information	Reason for rejecting study
578	Authors: Winberg J;. Title: What hygiene measures are advisable to prevent recurrent urinary tract infection and what evidence is there to support this advice?. Journal Name: Pediatric Nephrology. Year: 1994 Dec	Letter to the editor - no primary data
579	Authors: Blethyn AJ;Jenkins HR;Roberts R;Verrier JK;. Title: Radiological evidence of constipation in urinary tract infection. Journal Name: Archives of Disease in Childhood. Year: 1995 Dec	Half the number of controls (33) than cases (61). Not enough power to detect a difference.
580	Authors: Lopez MM;Castillo LA;Chavez JB;Ramones C;. Title: Hypercalciuria and recurrent urinary tract infection in Venezuelan children. Journal Name: Pediatric Nephrology. Year: 1999 Jun	Not enough information provided to indicate what number recurrence children are at. Normocalcuria may impact children differently eg. For those with 10 recurrent UTI's the impact of lowering calcium is likely to be different than those who have only had 2 UTIs.
581	Authors: Romanczuk W;Korczawski R;. Title: Chronic constipation: a cause of recurrent urinary tract infections. Journal Name: Turkish Journal of Pediatrics. Year: 1993 Jul	Study included children with chronic constipation and recurrent UTI - sub group analysis of guideline population. Not investigating constipation symptoms in all children with recurrent UTI. Not enough information on the number of recurrences. 2
49	Authors: Mingin GC;Hinds A;Nguyen HT;Baskin LS;. Title: Children with a febrile urinary tract infection and a negative radiologic workup: factors predictive of recurrence. [Review] [19 refs]. Journal Name: Urology. Year: 2004 Mar	Stated aims were not fulfilled - aimed to identify risk factors for recurrence, but only one factor (gender) analysed. Author contact details were not supplied. Follow up available on 69/78 (88%) However numbers reported out of 78. Gender details not supplied for the 69 followed up, so stated aim of analysing risk for gender cannot be calculated.
582	Authors: Jantunen ME;Saxen H;Salo E;Siitonen A;. Title: Recurrent urinary tract infections in infancy: relapses or reinfections?. Journal Name: Journal of Infectious Diseases. Year: 2002	Study provides a genotypic analysis of recurrent UTI analytes in children with pyelonephritis. Urinary isolates are a non-modifiable factor and this study can lend nothing new to clinical practice decisions.
293	Authors: Persad R;Kamineni S;Mouriquand PD;. Title: Recurrent symptoms of urinary tract infection in eight patients with refluxing ureteric stumps. Journal Name: British Journal of Urology. Year: 1994 Dec	Children recruited because of kidney damage secondary to VUR - not because of UTI.
583	Authors: Mingin GC;Nguyen HT;Baskin LS;. Title: Abnormal dimercapto-succinic acid scans predict an increased risk of breakthrough infection in children with vesicoureteral reflux. Journal Name: Journal of Urology. Year: 2004	Children with VUR recruited to investigate breakthrough UTI.
584	Authors: Sillen U;Hellstrom AL;Holmdahl G;Solsnes E;. Title: The voiding pattern in infants with dilating reflux. Journal Name: BJU International. Year: 1999 Jan	Not all children had UTI

Non-antibiotic strategies for managing recurrence

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Reference ID	Bibliographic Information	Reason for rejecting study
505	Authors: . Title: Cranberry and urinary tract infection.. Journal Name: Drug and Therapeutics Bulletin. Year: 2005 Mar	Review, but not systematic review of RCTs. Based on poor quality studies and opinion papers. Review covers three groups, adult women, children with neuropathic bladder and older men and women.
585	Authors: Casimir F;Fitzgerald DA;. Title: Is there a role for circumcision in boys with recurrent urinary tract infections?. Journal Name: Journal of Paediatrics and Child Health. Year: 2003 Aug	Single case report
586	Authors: Cason DL;Carter BS;Bhatia J;. Title: Can circumcision prevent recurrent urinary tract infections in hospitalized infants?. Journal Name: Clinical Pediatrics. Year: 2000 Dec	Study is in boys in neonatal intensive care.
587	Authors: Galland L;Adatto K;Doebele K;Granowetter L;Erde K;Campisi J;Koprowski P;. Title: Behavioral aspects of recurrent UTI. Journal Name: Journal of the American College Health Association. Year: 1977 Apr	Study in adult women
588	Authors: Gerasimov SV;. Title: Probiotic prophylaxis in pediatric recurrent urinary tract infections. Journal Name: Clinical Pediatrics. Year: 2004 Jan	Single case report
589	Authors: Lee B;Bhuta T;Craig J;Simpson J;. Title: Methenamine hippurate for preventing urinary tract infections. Journal Name: The Cochrane Library. Year: 2005	Cochrance review - of the 8 included studies patients included: 1. pregnant patients with asymptomatic bacteriuria 2. post-menopausal women 3. menstruating women 4. Adult patients (mean age 50.5 years) 5. Women post gynaecological operation 6. Male patients with traumatic spinal cord injury 7. Adult women undergoing a vaginal operation or expanded hysterectomy 8. women undergoing uterovaginal prolapse surgery.
504	Authors: Berger RE;. Title: Cranberries for preventing urinary tract infections. Journal Name: Journal of Urology. Year: 2005 Jun	Abstract of cochrance review
590	Authors: Jepson RG;Mihaljevic L;Craig J;. Title: Cranberries for preventing urinary tract infections.. Journal Name: The Cochrane Library. Year: 2005	Cochrance review - of the 8 included studies patients included: 1. Elderly women (mean age 78.5 years) 2. Children with neuropathic bladder 3. Elderly patients (mean age 81 years) 4. Adult women 5. Children with neuropathic bladder 6. Sexually active women 7. Sexually active women
499	Authors: Lynch DM;. Title: Cranberry for prevention of urinary tract infections.. Journal Name: American Family Physician. Year: 2004 Dec 1	Non-systematic review No primary data
591	Authors: . Title: Cranberries and UTI: the evidence. (Review of research on use of cranberries to prevent and relieve urinary tract infections. 9 refs). Journal Name: All Ireland J Nursing and Midwifery. Year:	Opinion paper
592	Authors: Foda MMR;Middlebrook PF;Gatfield CT;Potvin G;Wells G;Shillinger JF;. Title: Efficacy of Cranberry in Prevention of Urinary Tract Infection in a Susceptible Pediatric Population. Journal Name: The Canadian journal of urology. Year: 1995	Study in children with neuropathic bladder
593	Authors: Kontiokari T;Salo J;Eerola E;Uhari M;. Title: Cranberry juice and bacterial colonization in children--a placebo-controlled randomized trial. Journal Name:	Study evaluated effect of cranberry on nasopharyngeal and colonic flora

Reference ID	Bibliographic Information	Reason for rejecting study
	Clinical Nutrition. Year: 2005 Dec	
594	Authors: Super EA;Kemper KJ;Woods C;Nagaraj S;. Title: Cranberry use among pediatric nephrology patients. Journal Name: Ambulatory Pediatrics. Year: 2005 Jul	Non-comparative study. Describes cranberry use among paediatric patients and perceived benefits.
595	Authors: Barbosa-Cesnik CT;. Title: Cranberry Juice and Urinary Tract Infections. Journal Name: National Institut of Health. Year: 2006	Protocol of study in adult women
596	Authors: Hutchinson J;. Title: Do cranberries help prevent urinary tract infections?. [17 refs]. Journal Name: Nursing Times. Year: 2005 Nov 22	Review in adults.

Prophylaxis

Reference ID	Bibliographic Information	Reason for rejecting study
597	Authors: Beetz R;. Title: May we go on with antibacterial prophylaxis for urinary tract infections?. Journal Name: Pediatric Nephrology. Year: 2006	Review only - no primary data
598	Authors: Bollgren I;. Title: Antibacterial prophylaxis in children with urinary tract infection. Journal Name: Acta Paediatrica, International Journal of Paediatrics, Supplement. Year: 1999	Commentary only - no primary data
599	Authors: Centre for Reviews and Dissemination.;. Title: Evaluating the benefits of antimicrobial prophylaxis to prevent urinary tract infections in children: a systematic review (Structured abstract). Journal Name: Database of Abstracts of Reviews of Effectiveness. Year: 2006	CRD commentary on a systematic review.
600	Authors: Granados EA;. Title: [Which treatment should children with recurrent urinary infections, without anatomical anomalies, receive?]. Journal Name: Archivos espanoles de urologia. Year: 1998 May	Foreign language
601	Authors: Kaneko K;Ohtomo Y;Shimizu T;Yamashiro Y;Yamataka A;Miyano T;. Title: Antibiotic prophylaxis by low-dose cefaclor in children with vesicoureteral reflux. Journal Name: Pediatric Nephrology. Year: 2003 May	Non-comparative study 25/39 children had UTIs
434	Authors: Le Saux N;Pham B;Moher D;. Title: Evaluating the benefits of antimicrobial prophylaxis to prevent urinary tract infections in children: a systematic review.. Journal Name: CMAJ Canadian Medical Association Journal. Year: 2000	Systematic review where the majority of studies are cohort and case-control studies. Already have a Cochrane review of RCTs so this study does not provide additional information.
602	Authors: Montini G;. Title: Evaluation of the effectiveness of antibiotic prophylaxis in children with a history of upper urinary tract infections: a multicentre randomised study - Protocol. Journal Name: 2004 [No additional source data available]. Year:	Included in Cochrane review
85	Authors: Olbing H;Smellie JM;Jodal U;Lax H;. Title: New renal scars in children with severe VUR: a 10-year study of randomized treatment. Journal Name: Pediatric nephrology (Berlin, Germany). Year: 2003 Nov	Children randomised to prophylaxis or surgery. Does not answer question of whether prophylaxis is effective.
603	Authors: Seracini D;Materassi M;Danti A;. Title: Non-comparative open study on efficacy and safety of cefaclor as a prophylactic agent for urinary tract infections in children. Journal Name: Pediatria Medica e Chirurgica. Year: 1996	Foreign language

Reference ID	Bibliographic Information	Reason for rejecting study
604	Authors: Shakil A;Reed L;Wilder L;. Title: Do antibiotics prevent recurrent UTI in children with anatomic abnormalities?. Journal Name: Journal of Family Practice. Year: 2004	Commentary only - no primary data
605	Authors: Smith EM;Elder JS;Husmann DA;Peters CA;Belman AB;. Title: Double antimicrobial prophylaxis in girls with breakthrough urinary tract infections. Journal Name: Urology. Year: 1994	Not an RCT Case-series on girls with breakthrough infection
606	Authors: Stranieri G;Zampogna S;Ielapi V;Defilippo RG;Defilippo V;Cristofaro G;Galiano R;Capillo S;Madonna L;Cifala S;Ferro V;Rubino R;. Title: Cefixime for the prophylaxis of urinary tract infections in children with malformative uropathies: an open study. Journal Name: European Review for Medical and Pharmacological Sciences. Year: 2003 Mar	In children with UTI and urinary tract abnormalities
607	Authors: Wheeler D;Vimalachandra D;Hodson EM;Roy LP;Smith G;Craig JC;. Title: Antibiotics and surgery for vesicoureteric reflux: a meta-analysis of randomised controlled trials.. Journal Name: Archives of Disease in Childhood. Year: 2003 Aug	Does not investgate effectiveness of prophylaxis - will be included in surgery vs. reflux section
608	Authors: Williams G;Lee A;Craig J;. Title: Antibiotics for the prevention of urinary tract infection in children: a systematic review of randomized controlled trials. Journal Name: Journal of Pediatrics. Year: 2001	By the same authors who wrote the cochrane review. 3/5 papers included in the cochrane review, 1/5 excluded and 1/5 not mentioned.
609	Authors: Wingen AM;Koskimies O;Olbing H;Seppanen J;Tamminen-Mobius T;. Title: Growth and weight gain in children with vesicoureteral reflux receiving medical versus surgical treatment: 10-year results of a prospective, randomized study. International Reflux Study in Children (European Branch). Journal Name: Acta Paediatrica. Year: 1999 Jan	Children randomised to prophylaxis or surgery. Does not answer question of whether prophylaxis is effective. Will be included in surgery vs prophylaxis section
610	Authors: Stamm WE;. Title: Prevention of urinary tract infections. Journal Name: American Journal of Medicine. Year: 1984 May 15	Commentary only - no primary data
611	Authors: Baciulis V;. Title: Long-term cefadroxil prophylaxis in children with recurrent urinary tract infections [abstract]. Journal Name: Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. Year: 2003	Uncontrolled study
612	Authors: Coupris L;. Title: Antibiotic prophylaxis for surgery after vesico-ureteral reflux in children. Journal Name: Drugs. Year: 1988	Study does not compare prophylaxis with surgery
613	Authors: Cooper CS;Chung BI;Kirsch AJ;Canning DA;Snyder HM;. Title: The outcome of stopping prophylactic antibiotics in older children with vesicoureteral reflux.. Journal Name: Journal of Urology. Year: 2000 Jan	Case-series data only. Non-comparative
614	Authors: Rachmiel M;Aladjem M;Starinsky R;Strauss S;Villa Y;Goldman M;. Title: Symptomatic urinary tract infections following voiding cystourethrography. Journal Name: Pediatric Nephrology. Year: 2005 Oct	Non-comparative study

Evaluation of the structure of the urinary tract

Reference ID	Bibliographic Information	Reason for rejecting study
615	Authors: Weizer AZ;Silverstein AD;Auge BK;Delvecchio FC;Raj G;Albala DM;Leder R;Preminger GM;. Title: Determining the incidence of horseshoe kidney from	Not in children with UTI

Reference ID	Bibliographic Information	Reason for rejecting study
	radiographic data at a single institution. Journal Name: Journal of Urology. Year: 2003 Nov	
616	Authors: De Kort LMO;Uiterwaal CSPM;Beek EJA;Jan Nievelstein RA;Klijn AJ;De Jong TPVM;. Title: Reliability of voiding cystourethrography to detect urethral obstruction in boys. Journal Name: Urology. Year: 2004	Only 21/72 (30%) of boys with UTI as indication for VCUG but results not presented separately bor this group.
617	Authors: Karabacakoglu A;Karakose S;Ince O;Cobankara OE;Karalezli G;. Title: Diagnostic value of diuretic-enhanced excretory MR urography in patients with obstructive uropathy. Journal Name: European Journal of Radiology. Year: 2004 Dec	Age range of patients 8 to 71 yrs, data not separable by age groups. Also no mention of UTI.
618	Authors: Kilic S;Altinok MT;Ipek D;Beytur A;Baydinc YC;Gunes G;. Title: Color Doppler sonography examination of partially obstructed kidneys associated with ureteropelvic junction stone before and after percutaneous nephrolithotripsy: preliminary report. Journal Name: International Journal of Urology. Year: 2005 May	Age range of patients from 13 to 65 yrs thus outside scope of GL. Does not specify how many patients had UTI
619	Authors: Schoellnast H;Lindbichler F;Riccabona M;. Title: Sonographic diagnosis of urethral anomalies in infants: Value of perineal sonography. Journal Name: Journal of Ultrasound in Medicine. Year: 2004	Study sample includes only 15/88 (17%) of children with UTI; results not presented seperately by indication for imaging
620	Authors: Tsuchiya M;Hayashida M;Yanagihara T;Yoshida J;Takeda S;Tatsuma N;Tsugu H;Hino Y;Munakata E;Murakami M;. Title: Ultrasound screening for renal and urinary tract anomalies in healthy infants. Journal Name: Pediatrics International. Year: 2003	Study was population based and included all children visiting a paediatric dept (n=5700); did not investigate whether any included children had or have had UTI

Detecting vesicoureteric reflux

Reference ID	Bibliographic Information	Reason for rejecting study
621	Authors: Cooper CS;Madsen MT;Austin JC;Hawtrey CE;Gerard LL;Graham MM;Rushton HG;Cooper C;. Title: Bladder pressure at the onset of vesicoureteral reflux determined by nuclear cystometrogram. Journal Name: Journal of Urology. Year: 2003 Oct	Not in children with UTI
622	Authors: Best J;. Title: Pediatric voiding cystourethrogram. Journal Name: Images. Year: 2000	Guide to paediatric VCUG - no primary data
623	Authors: Elder JS;. Title: Imaging for vesicoureteral reflux--is there a better way?. Journal Name: Journal of Urology. Year: 2005 Jul	Editorial only - no primary data
624	Authors: Garcia-Nieto V;Siverio B;Monge M;Toledo C;Molini N;. Title: Urinary calcium excretion in children with vesicoureteral reflux. Journal Name: Nephrology Dialysis Transplantation. Year: 2003	Not specifically in children with UTI
625	Authors: Kosar A;Yesildag A;Oyar O;Perk H;Gulsoy U;. Title: Detection of vesico-ureteric reflux in children by colour-flow Doppler ultrasonography. Journal Name: BJU International. Year: 2003	Not in children with UTI
626	Authors: McLaren CJ;Simpson ET;. Title: Vesico-ureteric reflux in the young infant with follow-up direct radionuclide cystograms: The medical and surgical outcome at 5 years old. Journal Name: BJU International. Year: 2002	Not in children with UTI
627	Authors: Rubenstein JN;Maizels M;Kim SC;Houston JTB;. Title: The pic cystogram: A novel approach to identify 'occult' vesicoureteral reflux in children with febrile urinary tract infections. Journal Name: Journal of Urology.	Not all children were investigated for VUR because of a UTI. Cannot reliably construct a 2x2 table from the information provided.

Reference ID	Bibliographic Information	Reason for rejecting study
	Year: 2003 Jun	
628	Authors: Ascenti G;Zimbaro G;Mazziotti S;Chimenz R;Baldari S;Fede C;. Title: Vesicoureteral reflux: comparison between urosonography and radionuclide cystography. Journal Name: Pediatric Nephrology. Year: 2003 Aug	Did not use appropriate reference standard. Contrast enhanced colour Doppler voiding ultrasonography compared to Direct radionuclide voiding cystography.
629	Authors: D'Errico G;. Title: The role of nuclear medicine in evaluation of vesicoureteral reflux and/or reflux nephropathy.[erratum appears in Rays. 2003 Jan-Mar;28(1):118]. [Review] [26 refs]. Journal Name: Rays. Year: 2002 Apr	Non-systematic review No primary data
630	Authors: Darge K;. Title: Diagnosis of vesicoureteral reflux with ultrasonography. [Review] [70 refs]. Journal Name: Pediatric Nephrology. Year: 2002 Jan	Non-systematic review No primary data
631	Authors: Darge K;Trusen A;Troeger J;. Title: Diagnostic imaging of vesicoureteral reflux. [Review] [50 refs]. Journal Name: Rays. Year: 2002 Apr	Non-systematic review No primary data
632	Authors: Galia M;Midiri M;Pennisi F;Farina R;Bartolotta TV;De MM;Lagalla R;. Title: Vesicoureteral reflux in young patients: Comparison of voiding color Doppler US with echo enhancement versus voiding cystourethrography for diagnosis or exclusion. Journal Name: Abdominal Imaging. Year: 2004	Not all children had UTI 66/122 children underwent echo-enhanced Doppler cystosonography compared to VCUG following UTI, however numbers were not available for these children apart from the study group.
633	Authors: Hertz M;Rozenman J;. Title: Cystourethrography: technique, indications, and normal findings... part 1. Journal Name: Applied Radiology. Year: 1983	Practice points for VCUG. No primary data
634	Authors: Konda R;Sato H;Sakai K;Abe Y;Fujioka T;. Title: Urinary excretion of vascular endothelial growth factor is increased in children with reflux nephropathy. Journal Name: Nephron Clinical Practice. Year: 2004	Not in children with UTI (only in children with 'reflux nephropathy') Did not use appropriate reference standard. Urinary levels of vascular endothelial growth factor (VEGF) compared to DMSA.
635	Authors: Kopac M;Kenig A;Kljucevsek D;Kenda RB;. Title: Indirect voiding urosonography for detecting vesicoureteral reflux in children. Journal Name: Pediatric Nephrology. Year: 2005	Did not use appropriate reference standard. Echo-enhanced voiding ultrasonography compared to indirect voiding urosonography (IVUS)
636	Authors: Kuzmic AC;Brkljacic B;. Title: Color Doppler ultrasonography in the assessment of vesicoureteric reflux in children with bladder dysfunction. Journal Name: Pediatric Surgery International. Year: 2002	Not in children with UTI Colour Doppler ultrasonography compared VCUG to assess VUR in children with neuropathic bladder/sphincter dysfunction and non-neuropathic bladder.
637	Authors: Lee SK;Chang Y;Park NH;Kim YH;Woo S;. Title: Magnetic resonance voiding cystography in the diagnosis of vesicoureteral reflux: Comparative study with voiding cystourethrography. Journal Name: Journal of Magnetic Resonance Imaging. Year: 2005	Not all children had UTI. 14/20 children underwent Magnetic resonance voiding cystourethrography (MRVC) compared to VCUG following UTI, however numbers were not available for these children apart from the study group.
638	Authors: Mentzel HJ;Vogt S;John U;Kaiser WA;. Title: Voiding urosonography with ultrasonography contrast medium in children. Journal Name: Pediatric Nephrology. Year: 2002 Apr	Not all children had a UTI 67/118 children underwent Voiding urosonography compared to VCUG following UTI, however numbers were not available for these children apart from the study group.
639	Authors: Piaggio G;gl' Innocenti ML;Toma P;Calevo MG;Perfumo F;. Title: Cystosonography and voiding cystourethrography in the diagnosis of vesicoureteral reflux. Journal Name: Pediatric Nephrology. Year: 2003 Jan	Not all children had UTI 156/305 ureteral units underwent cystosonography (CSG) compared to VCUG following UTI, however numbers were not available for these children apart from the study group.

Reference ID	Bibliographic Information	Reason for rejecting study
640	Authors: Riccabona M;Mache CJ;Lindbichler F;. Title: Echo-enhanced color Doppler cystosonography of vesicoureteral reflux in children. Improvement by stimulated acoustic emission. Journal Name: Acta Radiologica. Year: 2003 Jan	Not all children had UTI 6/30 children underwent echo-enhanced Doppler cystosonography compared to VCUG following UTI, however numbers were not available for these children apart from the study group.
641	Authors: Tasic V;Todorovska S;. Title: Echo-enchanced voiding urosonography for detection of vesicoureteric reflux in children [2]. Journal Name: Pediatric Radiology. Year:	Letter to the Editor No primary data
642	Authors: Ascenti G;Zimbaro G;Mazziotti S;Chimenz R;Fede C;Visalli C;Scribano E;. Title: Harmonic US imaging of vesicoureteric reflux in children: Usefulness of a second generation US contrast agent. Journal Name: Pediatric Radiology. Year: 2004	only 29/80 of children included in study had diagnosis of UTI
643	Authors: Berrocal T;Gaya F;Arjonilla A;. Title: Vesicoureteral reflux: Can the urethra be adequately assessed by using contrast-enhanced voiding US of the bladder?. Journal Name: Radiology. Year: 2005	Nearly half of study sample (44%) do not have UTI
644	Authors: Bhatnagar V;Mitra DK;Agarwala S;Kumar R;Patel C;Malhotra AK;Gupta AK;. Title: The role of DMSA scans in evaluation of the correlation between urinary tract infection, vesicoureteric reflux, and renal scarring. Journal Name: Pediatric Surgery International. Year: 2002	Does not compare DMSA with MCUG for VUR (compares DMSA with US for scarring)
645	Authors: Darge K;Moeller R;Trusen A;Butter F;Gordjani N;Riedmiller H;. Title: Diagnosis of vesicoureteric reflux with low-dose contrast-enhanced harmonic ultrasound imaging. Journal Name: Pediatric Radiology. Year: 2005	population includes 25/55 (45%) of chidlren without UTI
646	Authors: Grmek M;Fettich J;. Title: The importance of follow-up of children with vesicoureteral reflux grade 1. Journal Name: Acta Paediatrica. Year:	Did not use appropriate reference standard. Probability that cyclic radionuclide cystograhy predicts VUR.
647	Authors: Jose TE;Mohiudheen H;Patel C;Kumar R;Chandrashekar B;Malhothra A;. Title: Direct radionuclide cystography by supra-pubic puncture: Comparison with conventional voiding cystourethrography. Journal Name: Nuclear Medicine Communications. Year: 2004	Not all children had UTI. 1/43 children underwent supra-pubic Direct radionuclide cystography (SDRC) compared to VCU following UTI, however numbers were not available for this child apart from the study group
648	Authors: Kumar R;Aggarwal B;Aggarwal A;Ranjan BB;Aggarwal SK;. Title: Spectrum of diseases on micturating cystourethrography in pediatric patients presenting with recurrent urinary tract infections. Journal Name: Asian Oceanian Journal of Radiology. Year: 2002	Non-comparative study. Describes VUR and other pathologies in children referred for a MCU.
649	Authors: Leung VY;Metreweli C;Yeung CK;. Title: Immature ureteric jet doppler patterns and urinary tract infection and vesicoureteric reflux in children. Journal Name: Ultrasound in Medicine and Biology. Year: 2002 Jul	study investigates correlations bet immature ureteric jet doppler patterns and UTI and VUR; does not investigate immature patterns as a method for detecting VUR
650	Authors: Mahant S;Friedman J;MacArthur C;. Title: Renal ultrasound findings and vesicoureteral reflux in children hospitalised with urinary tract infection. Journal Name: Archives of Disease in Childhood. Year: 2002	Included in HTA
651	Authors: McEwing RL;Anderson NG;Hellewell S;Mitchel J;. Title: Comparison of echo-enhanced ultrasound with fluoroscopic MCU for the detection of vesicoureteral reflux in neonates. Journal Name: Pediatric Radiology. Year: 2002	Not all children had a UTI. 1/100 children underwent Echo-enhanced ultrasonographycompared to MCU following UTI.
652	Authors: Medina LS;Aguirre E;Altman NR;. Title: Vesicoureteral reflux imaging in children: comparative cost analysis. Journal Name: Academic Radiology. Year: 2003 Feb	Cost-analysis only

Reference ID	Bibliographic Information	Reason for rejecting study
[653]	Authors: Muensterer OJ;. Title: Comprehensive ultrasound versus voiding cysturethrography in the diagnosis of vesicoureteral reflux. Journal Name: European Journal of Pediatrics. Year: 2002	Not all children had a UTI 101/193 children underwent renal ultrasound compared to VCUG following UTI, however numbers were not available for these children apart from the study group.
[654]	Authors: Nakamura M;Wang Y;Shigeta K;Shinozaki T;Taniguchi N;Itoh K;. Title: Simultaneous voiding cystourethrography and voiding urosonography: An in vitro and in vivo study. Journal Name: Clinical Radiology. Year:	No information about whether children had a UTI. Inclusion criteria are diagnosed cases of VUR. Sub-set of patients from[655] which has been included.
[656]	Authors: Novljan G;Kenig A;Rus R;Kenda RB;. Title: Cyclic voiding urosonography in detecting vesicoureteral reflux in children. Journal Name: Pediatric Nephrology. Year: 2003 Oct	Not all children had a UTI and did not use appropriate reference standard. 5/50children underwent conventional voiding ultrasound compared to cyclic voiding ultrasound following UTI, however numbers were not available for these children apart from the study group.
[657]	Authors: Papadopoulou F;Efremidis SC;Economou A;Badouraki M;Panteleli M;Papachristou F;Soteriou I;. Title: Cyclic voiding cystourethrography: Is vesicoureteral reflux missed with standard voiding cystourethrography?. Journal Name: European Radiology. Year: 2002 Mar	Study sample (n=275) includes children (10%) without UTI
[658]	Authors: Valentini AL;De Gaetano AM;Destito C;Marino V;Minordi LM;Marano P;. Title: The accuracy of voiding urosonography in detecting vesico-ureteral reflux: a summary of existing data. Journal Name: European Journal of Pediatrics. Year: 2002 Jul	Age range of participants from included studies not specified. Indications for VUR were not limited to UTI but included ante- and post natal pyelectasis, myelomeningocele, spina bifida, noturnal enuresis, multicystic kidney, single kidney, and hypospadias
[659]	Authors: Fettich J;Colarinha P;Fischer S;Frokier J;Gordon I;Hahn K;Kabasakal L;Mann M;Mitjavila M;Olivier P;Piepsz A;Porn U;Roca I;Sixt R;Van VJ;. Title: Guidelines for direct radionuclide cystography in children. Journal Name: European Journal of Nuclear Medicine and Molecular Imaging. Year: 2003 May	Guidelines for radionuclide cystography in children No primary data
[660]	Authors: Bower G;Lovegrove FT;Geijsel H;Van der SA;Guelfi G;. Title: Comparison of 'direct' and 'indirect' radionuclide cystography. Journal Name: Journal of Nuclear Medicine. Year: 1985 May	Included in HTA
[661]	Authors: De SC;De B;Keuppens F;Desprechins B;Verboven M;Piepsz A;. Title: How good is technetium-99m mercaptoacetyltriglycine indirect cystography?. Journal Name: European Journal of Nuclear Medicine. Year: 1994 Mar	Included in HTA
[662]	Authors: Hedman PJ;Kempi V;Voss H;. Title: Measurement of vesicoureteral reflux with intravenous 99mTc-DTPA compared to radiographic cystography. Journal Name: Radiology. Year: 1978 Jan	No reference standard used.
[663]	Authors: Chevalier I;Gauthier M;Leroy S;Gendrel D;Breart G;Chalumeau M;. Title: Procalcitonin and vesicoureteral reflux in children with urinary tract infection... Leroy S, Adamsbaum C, Marc E et al. Procalcitonin as a predictor of vesicoureteral reflux in children with a first febrile urinary tract infection. Pediatrics. 2005;115(6). Available at: www.pediatrics.org/cgi/content/full/115/6/e706. Journal Name: Pediatrics. Year: 2005	Letter to the editor, no primary data
[664]	Authors: Leroy S;Marc E;Adamsbaum C;Gendrel D;Breart G;Chalumeau M;. Title: Prediction of vesicoureteral reflux after a first febrile urinary tract infection in children: validation of a clinical decision rule.[see comment]. Journal	Clinical decision rule validation

Reference ID	Bibliographic Information	Reason for rejecting study
	Name: Archives of Disease in Childhood. Year: 2006 Mar	
665	Authors: Thompson M;Simon SD;Sharma V;Alon US;. Title: Timing of follow-up voiding cystourethrogram in children with primary vesicoureteral reflux: Development and application of a clinical algorithm. Journal Name: Pediatrics. Year: 2005	Study develops an algorithm for VCUG in children who have already been diagnosed with VUR

Detecting renal parenchymal defects

Reference ID	Bibliographic Information	Reason for rejecting study
666	Authors: Araujo CB;Barroso JU;Barroso VA;Vinhaes AJ;Jacobino M;Calado A;Zerati FM;. Title: Comparative study between intravenous urography and renal scintigraphy with DMSA for the diagnosis of renal scars in children with vesicoureteral reflux. Journal Name: International Braz J Urol. Year: 2003	No indication as to whether children had a previous UTI.
667	Authors: Atasever T;Ozkaya O;Abamor E;Soylemezoglu O;Buyan N;Unlu M;. Title: ^{99m}Tc ethylene dicysteine scintigraphy for diagnosing cortical defects in acute pyelonephritis: A comparative study with ^{99m}Tc dimercaptosuccinic acid. Journal Name: Nuclear Medicine Communications. Year: 2004	Numbers nor provided to assess diagnostic accuracy of 99mTc ethylene dicysteine scintigraphy. Only positive results provided (a) and no way of assessing number of false negatives.
668	Authors: Baxter H;. Title: Renal scarring and the best imaging modalities for detection. Journal Name: Synergy. Year: 2004	Commentary only - no primary data
644	Authors: Bhatnagar V;Mitra DK;Agarwala S;Kumar R;Patel C;Malhotra AK;Gupta AK;. Title: The role of DMSA scans in evaluation of the correlation between urinary tract infection, vesicoureteric reflux, and renal scarring. Journal Name: Pediatric Surgery International. Year: 2002	Not a diagnostic study for detecting VUR.
669	Authors: Calado AA;Barroso JU;Barroso VA;Souza AS;Filho MZ;. Title: Ultrasound evaluation of renal scarring in children with vesicouretral reflux. Journal Name: Brazilian Journal of Urology. Year: 2002	Analyses the accuracy of renal ultrasound in detecting renal scars in patients who had VUR, not in children with UTI.
670	Authors: Chromek M;Tullus K;Hertting O;Jaremko G;Khalil A;Li Y;Brauner A;. Title: Matrix metalloproteinase-9 and tissue inhibitor of metalloproteinases-1 in acute pyelonephritis and renal scarring. Journal Name: Pediatric Research. Year: 2003 Feb 19	Not a diagnostic study - presents correlations only.
671	Authors: Hiraoka M;Hashimoto G;Tsuchida S;Tsukahara H;Ohshima Y;Mayumi M;. Title: Early treatment of urinary infection prevents renal damage on cortical scintigraphy. Journal Name: Pediatric Nephrology. Year: 2003 Feb	Not a study of diagnostic accuracy - refers to treatment timing and will be included in treatmet section of the guideline.
672	Authors: Imperiale A;Olianti C;Sestini S;Materassi M;Daniela S;Ienuso R;La CG;. Title: 123-I-hippuran renal scintigraphy with evaluation of single-kidney clearance for predicting renal scarring after acute urinary tract infection: Comparison with 99m-Tc-DMSA scanning. Journal Name: Journal of Nuclear Medicine. Year: 2003	I-hippuran scans are not performed in UK and single kidney clearance rates are not calculated.
673	Authors: Kibar M;Yapar Z;Noyan A;Anarat A;. Title: Technetium-99m-N,N-ethylenedicysteine and Tc-99m DMSA scintigraphy in the evaluation of renal parenchymal abnormalities in children. Journal Name: Annals of Nuclear Medicine. Year: 2003	Children were evaluated for scarring because of abnormalities, not because of UTI

Reference ID	Bibliographic Information	Reason for rejecting study
674	Authors: Kobayashi H;Miyakita H;Yamataka A;Koga H;Lane GJ;Miyano T;. Title: Serum basic fibroblast growth factor as a marker of reflux nephropathy. Journal Name: Journal of Pediatric Surgery. Year: 2004	Not a study about diagnostic accuracy. Not specifically in children with UTI
79	Authors: Moorthy I;Easty M;McHugh K;Ridout D;Biassoni L;Gordon I;. Title: The presence of vesicoureteric reflux does not identify a population at risk for renal scarring following a first urinary tract infection. Journal Name: Archives of Disease in Childhood. Year: 2005	Study assumes that VUR indicates scarring. 2x2 table compared scarring found on DMSA (reference standard) with VUR found on cystogram. This study design would only be valid if we were 100% sure that VUR was the cause of scarring.
675	Authors: Padmakumar B;Carfy HM;Hughes DA;Judd BA;. Title: Role of intravenous urogram in investigation of urinary tract infection: An observational study. Journal Name: Postgraduate Medical Journal. Year: 2004	Observational study only.
676	Authors: Taskinen S;Ronnholm K;. Title: Post-pyelonephritic renal scars are not associated with vesicoureteral reflux in children. Journal Name: Journal of Urology. Year: 2005	Information not provided to construct a 2x2 table

Surgical management of vesicoureteric reflux

Reference ID	Bibliographic Information	Reason for rejecting study
607	Authors: Wheeler D;Vimalachandra D;Hodson EM;Roy LP;Smith G;Craig JC;. Title: Antibiotics and surgery for vesicoureteric reflux: a meta-analysis of randomised controlled trials.. Journal Name: Archives of Disease in Childhood. Year: 2003 Aug	Additional publication of Cochrane review material
677	Authors: Yu TJ;Chen W;Chen HY;Belman AB;. Title: Early versus late surgical management of fetal reflux nephropathy. Journal Name: Journal of Urology. Year: 1997	Non-randomised study.
678	Authors: Yu TJ;Chen WF;. Title: Surgical management of grades III and IV primary vesicoureteral reflux in children with and without acute pyelonephritis as breakthrough infections: A comparative analysis. Journal Name: Journal of Urology. Year: 1997	Comparative study, but not an RCT.
679	Authors: Gordjani N;Frankenschmidt A;Zimmerhackl LB;Brandis M;. Title: Subureteral collagen injection versus antireflux surgery in primary vesico-ureteral reflux grade III. Journal Name: European Journal of Pediatrics. Year: 1996	Non-comparative study
680	Authors: Arima M;Matsui T;Ogino T;Shimada K;Hosokawa S;Mori Y;Ikoma F;. Title: Vesicoureteral reflux in infants under one year old: Follow-up study and consideration on development of renal scarring. Journal Name: Urology. Year: 1993	Not an RCT
681	Authors: Blyth B;Passerini-Glazel G;Camuffo C;Snyder III HM;Duckett JW;Allen TD;. Title: Endoscopic incision of ureteroceles: Intravesical versus ectopic. Journal Name: Journal of Urology. Year: 1993	Case-series study reporting experiences with incision as initial therapy for ureterocles.
609	Authors: Wingen AM;Koskimies O;Olbing H;Seppanen J;Tamminen-Mobius T;. Title: Growth and weight gain in children with vesicoureteral reflux receiving medical versus surgical treatment: 10-year results of a prospective, randomized study. International Reflux Study in Children	Included in Cochrane review

	(European Branch). Journal Name: Acta Paediatrica. Year: 1999 Jan	
682	Authors: Jodal U;Hansson S;Hjalmas K;. Title: Medical or surgical management for children with vesico-ureteric reflux?. Journal Name: Acta Paediatrica. Year: 1999	Included in Cochrane review.
683	Authors: . Title: Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children: five years' observation. Birmingham Reflux Study Group. Journal Name: British medical journal (Clinical research ed). Year: 1987 Jul	Included in Cochrane review.
684	Authors: Aboutaleb H;Bolduc S;Upadhyay J;Farhat W;Bagli DJ;Khoury AE;. Title: Subureteral polydimethylsiloxane injection versus extravesical reimplantation for primary low grade vesicoureteral reflux in children: A comparative study. Journal Name: Journal of Urology. Year: 2003	Compared two surgical methods.
685	Authors: Centre for Reviews and Dissemination.;. Title: Antibiotics and surgery for vesicoureteric reflux: a meta-analysis of randomised controlled trials (Structured abstract). Journal Name: Database of Abstracts of Reviews of Effectiveness. Year: 2005	CRD commentary on a systematic review
686	Authors: Duckett JW;Walker RD;Weiss R;. Title: Surgical results: International Reflux Study in Children - United States branch. Journal Name: Journal of Urology. Year: 1992	Part of the International reflux study - included in Cochrane review.
687	Authors: Esbjorner E;Hansson S;Jakobsson B;. Title: Management of children with dilating vesico-ureteric reflux in Sweden. Journal Name: Acta Paediatrica. Year: 2004	Not an RCT.
688	Authors: Fanos PV;Cataldi PL;. Title: Antibiotics or surgery for vesicoureteric reflux in children. Journal Name: Lancet. Year:	Commentary only - no primary data
689	Authors: Hjalmas K;Lohr G;Tamminen-Mobius T;Seppanen J;Olbing H;Wikstrom S;. Title: Surgical results in the International Reflux Study in Children (Europe). Journal Name: The Journal of urology. Year: 1992 Nov	Included in Cochrane review.
690	Authors: Holland NH;Kazee M;Duff D;McRoberts JW;. Title: Antimicrobial prophylaxis in children with urinary tract infection and vesicoureteral reflux. Journal Name: Reviews of infectious diseases. Year: 1982	Included in Cochrane review.
691	Authors: Iitaka K;Motoyama O;Moriya S;Endo T;Sakai T;. Title: Management of vesicoureteral reflux in children. Journal Name: Clinical and Experimental Nephrology. Year: 2000	Non-randomised trial
692	Authors: Manunta A;Patard JJ;Guille F;Moussa MA;Morin G;Guiraud P;Lobel B;. Title: Recurrent pyelonephritis without vesicoureteral reflux: Is there a role for an antireflux procedure?. Journal Name: Journal of Endourology. Year: 2001	Study in adults
693	Authors: Olbing H;Hirche H;Koskimies O;Lax H;Seppanen U;Smellie JM;Tamminen-Mobius T;Wikstad I;. Title: Renal growth in children with severe vesicoureteral reflux: 10-year prospective study of medical and surgical treatment: the International Reflux Study in Children (European branch). Journal Name: Radiology. Year: 2000 Sep	Included in Cochrane review.
694	Authors: Piepsz A;Tamminen-Mobius T;Reiners C;Heikkila J;Kivisaari A;Nilsson NJ;Sixt R;Risdon RA;Smellie JM;Soderborg B;. Title: Five-year study of medical or surgical treatment in children with severe vesico-ureteral reflux dimercaptosuccinic acid findings. International Reflux Study Group in Europe. Journal Name: European Journal of Pediatrics. Year: 1998 Sep	Included in Cochrane review.

695	Authors: Rahmani MA;Shakeel MM;Chaudhary IA;. Title: Vesico-ureteric reflux in children. Journal Name: Journal of the College of Physicians and Surgeons Pakistan. Year: 2002	Non-randomised trial
696	Authors: Roseau E;. Title: [Vesico-ureteral reflux and nephropathy in the child: medical or surgical treatment?]. Journal Name: Presse medicale (Paris, France :. Year: 2001	Foreign language
697	Authors: Smellie JM;Tamminen-Mobius T;Olbing H;Claesson I;Wikstad I;Jodal U;Seppanen U;. Title: Five-year study of medical or surgical treatment in children with severe reflux: radiological renal findings. The International Reflux Study in Children. Journal Name: Pediatric nephrology (Berlin, Germany). Year: 1992 May	Included in Cochrane review.
698	Authors: Smellie JM;. Title: Commentary: management of children with severe vesicoureteral reflux. Journal Name: The Journal of urology. Year: 1992 Nov	Commentary only - no primary (original) data
699	Authors: Smellie JM;Tamminen-Mobius T;Olbing H;Claesson I;Wikstad I;Jodal U;Seppanen U;. Title: [Radiologic findings in the kidney of children with severe reflux. Five-year comparative study of conservative and surgical treatment]. Journal Name: Der Urologe Ausg A. Year: 1993 Jan	Foreign language
700	Authors: Smellie JM;Jodal U;Lax H;Tamminen MT;Hirche H;Olbing H;. Title: Outcome at 10 years of severe vesicoureteric reflux managed medically: Report of the international reflux study in children. Journal Name: Journal of Pediatrics. Year: 2001	Part of the International reflux study - included in the Cochrane review.
701	Authors: Tamminen-Mobius T;Brunier E;Ebel KD;Lebowitz R;Olbing H;Seppanen U;Sixt R;. Title: Cessation of vesicoureteral reflux for 5 years in infants and children allocated to medical treatment. The International Reflux Study in Children. Journal Name: The Journal of urology. Year: 1992 Nov	Included in Cochrane review.
702	Authors: White RH;. Title: Management of urinary tract infection and vesicoureteric reflux in children. 1. Operative treatment has no advantage over medical management. [Review] [9 refs]. Journal Name: BMJ. Year: 1990 May 26	Commentary only - no primary data
703	Authors: Reddy PP;Evans MT;Hughes PA;Dangman B;Cooper J;Lepow ML;Calvano CJ;Mandell J;. Title: Antimicrobial prophylaxis in children with vesico-ureteral reflux: a randomized prospective study of continuous therapy vs intermittent therapy vs surveillance. Journal Name: Pediatrics. Year: 1997	Included in Cochrane review.
704	Authors: Beetz R;Schulte-Wissermann H;Troger J;Riedmiller H;Mannhardt W;Schofer O;Hohenfellner R;. Title: Long-term follow-up of children with surgically treated vesicorenal reflux: Postoperative incidence of urinary tract infections, renal scars and arterial hypertension. Journal Name: European Urology. Year: 1989	Not an RCT
705	Authors: . Title: Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux: two years' observation in 96 children. Journal Name: British medical journal (Clinical research ed). Year: 1983 Jul	Included in Cochrane review.
59	Authors: Smellie JM;Barratt TM;Chantler C;Gordon I;Prescod NP;Ransley PG;Woolf AS;. Title: Medical versus surgical treatment in children with severe bilateral vesicoureteric reflux and bilateral nephropathy: A randomised trial. Journal Name: Lancet. Year:	Included in Cochrane review.

[706]	Authors: Belloli G;Bolla G;Cappellari F;Musi L;. Title: Long-term follow up of surgically treated primary vesicorenal reflux. Journal Name: Pediatric Surgery International. Year: 1994	Non-comparative study
[707]	Authors: Capozza N;Caione P;. Title: Dextranomer/hyaluronic acid copolymer implantation for vesico-ureteral reflux: a randomized comparison with antibiotic prophylaxis. Journal Name: Journal of Pediatrics. Year: 2002 Feb	Included in Cochrane review
[708]	Authors: Elder JS;Diaz M;Caldamone AA;Cendron M;Greenfield S;Hurwitz R;Kirsch A;Koyle MA;Pope J;Shapiro E;. Title: Endoscopic therapy for vesicoureteral reflux: a meta-analysis. I. Reflux resolution and urinary tract infection. Journal Name: Journal of Urology. Year: 2006 Feb	Outside scope
[709]	Authors: Venhola M;Huttunen NP;Uhari M;. Title: Meta-analysis of vesicoureteral reflux and urinary tract infection in children. Journal Name: Scandinavian Journal of Urology and Nephrology. Year: 2006	Although meta-analysis was published in 2006, searches were conducted between 1966 and 1998. Of the trials included, 2 were not RCTs, and three were included in the cochrane review.
[57]	Authors: Jodal U;. Title: Ten-year results of randomized treatment of children with severe vesicoureteral reflux. Final report of the International Reflux Study in Children. Journal Name: Pediatric Nephrology. Year: 2006	Aim of paper is to present the overall results of the International Reflux Study. 10 year results have been reported in more detail elsewhere and are included in the Cochrane review.
[710]	Authors: Mevorach RA;Hulbert WC;Rabinowitz R;Kennedy WA;Kogan BA;Kryger JV;Caldamone A;Clark WR;Kaplan GW;Durkee CT;Elder JS;. Title: Results of a 2-year multicenter trial of endoscopic treatment of vesicoureteral reflux with synthetic calcium hydroxyapatite. Journal Name: Journal of Urology. Year: 2006 Jan	Outside scope
[711]	Authors: Weiss R;Duckett J;Spitzer A;. Title: Results of a randomized clinical trial of medical versus surgical management of infants and children with grades III and IV primary vesicoureteral reflux (United States). Journal Name: Journal of Urology. Year: 1992	Included in Cochrane review

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