National Institute for Health and Care Excellence

Pneumonia: diagnosis and management (update)

[H] Evidence reviews for the clinical and cost effectiveness of monitoring biomarkers to determine when to de-escalate or change place of care for people in hospital with CAP or HAP.

NICE guideline [number]
Evidence reviews underpinning recommendations 1.4.1, 1.11.7 to 1.11.8 in the NICE guideline

April 2025

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1 Biomarkers for de-escalating care

1.1 Review question

In people in hospital with a diagnosis of community- or hospital-acquired pneumonia, what is the clinical and cost effectiveness of monitoring C-reactive protein or procalcitonin and other biomarkers (or combinations of biomarkers) in addition to clinical observation in helping to determine when to deescalate or change treatment and when to change the place of care (for example, from ICU to non-ICU care or discharge from hospital)?

1.1.1 Introduction

Patients with community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) who are admitted to hospital are currently monitored by routine physiological observations, repeat clinical assessments and blood tests. Evidence of improvement in the patient's condition informs decisions about when to stop antibiotic therapy and when to discharge from hospital. Absence of improvement or deterioration guides change in empirical antibiotic therapy and patient management. Currently this approach is unstructured, with the potential for over or under treatment with antibiotics and inappropriate discharge decisions. A more objective assessment using biomarkers such as C-reactive protein (CRP) and procalcitonin may be better than clinical observations and judgement alone when making decisions about managing patients with pneumonia (e.g., stopping antibiotics, discharging patients).

The aim of this review is to evaluate the effectiveness of CRP, procalcitonin, or other biomarkers in patients hospitalised with pneumonia for guiding patient management and de-escalating care, such as determining whether it is safe or appropriate stop or change antibiotic treatment, and whether to discharge from hospital.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Population	**Inclusion** Babies over 28 days (corrected gestational age), children, young people (age <18 years) and adults (≥18 years) with pneumonia (community or hospital acquired) requiring management in hospital. • CAP is defined as pneumonia that is acquired outside hospital • HAP is defined as pneumonia that occurs 48 hours or more after admission to hospital and is not incubating at hospital admission, or within 10 days of a previous hospital admission for a different problem. Note: studies that include a broader population (e.g., sepsis, LRTI) will be included if: (a) they give results stratified for pneumonia; or (b) ≥ 75% patients have pneumonia **Exclusion** • Babies up to and including 28 days (corrected gestational age) • People with COVID-19 pneumonia

	• People who acquire pneumonia while intubated (ventilator-associated pneumonia) • People who are severely immune-compromised (have a primary immune deficiency or secondary immune deficiency related to HIV infection, or severe drug or systemic disease-induced immunosuppression, for example, people who have taken immunosuppressant cancer therapy or undergone organ transplantation). • People in whom pneumonia is an expected terminal event. • People with non-pneumonic infective exacerbations of bronchiectasis. • People with non-pneumonic infective exacerbations of chronic obstructive pulmonary disease. • People with pneumonia associated with cystic fibrosis. • People with aspiration pneumonia as a result of inhaling a large bolus of gastric contents.
Interventions	Usual care (clinical observation) plus biomarkers of interest: • C-reactive protein • Procalcitonin • Neutrophil/lymphocyte ratio We will include serial measurements or single test after initial admission assessment. CRP tests may be comparing results on e,g., day 3 to day 1, whereas PCT may be tested daily. Absolute values and change-from-baseline values will be included. All thresholds investigated will be reported to aid identification of the optimum cut-off. Threshold definitions will be according to study protocols – but differences will be noted. The focus is on use of these biomarkers to stop / change / deescalate care in patients already diagnosed and hospitalised with pneumonia; not to inform diagnosis or decision to admit to hospital or initiate antibiotics.
Comparator	Usual care (clinical observation)
Outcomes	**For the effectiveness evidence:** **Primary outcomes** • Mortality within 30 days • Antibiotic type (broad or narrow spectrum) and duration • ICU admission • Need for invasive ventilation • Length of hospital stay • Length of ICU stay • Hospital re-admission within 30 days **Secondary outcomes** • Health related quality of life (HRQoL) • Adverse events (including recurrence of pneumonia during admission; recurrence of respiratory symptoms; development of sepsis or severe shock; development of necrotising pneumonia) • Hospital acquired infections including *C. difficile* **For the prognostic evidence:** Hazard ratios, odds ratios and relative risks.

	Where reported we will include: • Sens/spec • LR+/- • AUC.
Study type	**Effectiveness evidence** • Systematic reviews of RCTs and RCTs • Non-randomised controlled trials **Prognostic evidence** • Prospective cohort studies • Retrospective cohort studies, if insufficient prospective cohort studies

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

For studies where only sensitivity and specificity were reported, likelihood ratios were calculated by the NICE development team. As 95% confidence intervals could not be calculated for these outcomes, it was not possible to apply GRADE, because imprecision could not be assessed without measures of variance and the agreed approach was to not apply GRADE unless all domains could be assessed. The sensitivity, specificity, positive and negative likelihood ratios only are reported in tables 9, 11, 13, 18 and 19; no GRADE summaries or GRADE tables are provided for these outcomes.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.3.1 Search methods

Each evidence review for this guideline had a search conducted in three parts. Part 1 was a single search for all systematic reviews relating to pneumonia published since 2014 that was screened for relevance to all the review questions. Part 2 was tailored to each evidence review. Part 3 covered the cost effectiveness elements of all review questions in a single search.

The searches for systematic reviews on all pneumonia topics were run on 20 November 2023 and re-run on 15 October 2024 in Cochrane Database of Systematic Reviews (CDSR) (Wiley) and Epistemonikos (https://www.epistemonikos.org).

The searches for effectiveness and prognostic evidence were run on 23 February 2024. These searches were done in two parts so that different date limits could be applied to the appropriate population (adults since March 2014 and children and young people with no date limits).

The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Embase (Ovid); and MEDLINE ALL (Ovid). Limits were applied to remove animal studies, case reports, conference abstracts, editorials, empty registry entries,

letters, news items and references not published in the English language. Study-type filters were used in MEDLINE and Embase to limit to RCTs and prognostics.

The database searches were supplemented with additional search methods. Reference list checking and forward citation searching were conducted on Web of Science Core Collection on 22 February 2024 using seed references identified from the scoping searches, the papers included in CG191 and the search for systematic reviews. Reference list checking was also conducted using systematic reviews identified in the searches for effectiveness evidence.

The searches for cost effectiveness evidence were run on 20 November 2023 and re-run on 14 October 2024 for papers published since 2014. The following databases were searched: Econlit (Ovid); Embase (Ovid); International HTA Database (https://database.inahta.org); MEDLINE ALL (Ovid); and NHS Economic Evaluation Database (NHS EED) (CRD). The same limits as in the effectiveness search were used. The validated NICE Cost Utility Filter was used on MEDLINE and Embase. Validated NICE filters were used in MEDLINE and Embase to remove references exclusively set in countries that are not OECD members.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement.

Explanatory notes and full search strategies for each database are provided in appendix B.

1.1.3.2 Protocol deviations

The committee listed a number of primary outcomes that can be used to indicate pneumonia severity or disease progression e.g. ICU admission or need for invasive ventilation. In the original protocol they did not specify pneumonia severity as a primary outcome as they considered these proxy measures sufficient but later agreed that it would also be useful to extract data for this outcome in the studies that reported it, so pneumonia severity was added as a primary outcome via a protocol deviation. The committee also noted that several studies reported composite outcomes that were a combination of primary outcomes listed in the protocol that were indicators of overall adverse outcomes (ICU admission, need for invasive ventilation, mortality). They agreed to include composite outcome data on the basis that the components were all included primary outcomes. The committee also decided to add clinical cure as a protocol deviation for the effectiveness evidence, because this outcome would give them useful information about the appropriateness of reducing antibiotics.

Area under the curve (AUC) was listed as an outcome in the original protocol, but to manage the volume of evidence, this outcome was removed from the protocol as a protocol deviation. It was felt that other outcomes (mean difference, relative risk, sensitivity and specificity) were of most interest for decision making, so were prioritised over AUC.

1.1.4 Effectiveness and Prognostic evidence

1.1.4.1 Included studies - adults

For adults, a systematic search carried out to identify potentially relevant studies found 3,535 references (see appendix B for the literature search strategy). These 3,535 references were screened at title and abstract level against the review protocol, with 3,440 excluded at this level. The full texts of 95 papers were ordered for closer inspection; 32 of these were randomised studies of interventions and 63 were cohort studies. 30 of these studies met the

criteria specified in the review protocol (appendix A). For a summary of the 30 included studies see table 2 for the effectiveness evidence and table 3 for the prognostic evidence.

The effectiveness evidence included 4 RCTs and 3 non-randomised historically controlled studies focusing on the safety and effectiveness of using a procalcitonin-guided algorithm to reduce the duration of antibiotic treatment, relative to usual care. In all included studies, usual care consisted of standard antibiotic treatment strategies and clinical observation, with most of the studies also referencing the use of local practice guidelines to inform care. No studies were identified that investigated the use of biomarkers for other aspects of care de-escalation such as discharge from ICU or discharge home.

The prognostic evidence included 23 prospective cohort studies reporting on the association between levels of the 3 biomarkers of interest and key clinical outcomes (mortality, need for ICU admission, CAP severity and adverse outcomes). Retrospective cohort studies were excluded as there were sufficient prospective cohort studies; this was in line with the step-down approach to study selection specified in the protocol.

1.1.4.2 Included studies – babies, children and young people

For babies, children and young people, a systematic search identified 1,021 potentially relevant references (see appendix B for the literature search strategy). Title and abstract screening of these 1,021 references identified 45 potential includes, which were ordered at full text for closer review; 976 records were excluded at this stage. Full text screening identified 5 papers that met the inclusion and exclusion criteria specified in the review protocol (appendix A); 40 records were excluded at full text screening. 2 included studies were RCTs focusing on the safety and effectiveness of using a procalcitonin-guided algorithm to reduce the duration of antibiotic treatment, relative to usual care. In all included studies, usual care consisted of standard antibiotic treatment strategies and clinical observation. No studies were identified that investigated the use of biomarkers for other aspects of care de-escalation such as discharge from ICU or discharge home. The remaining 3 included studies were prospective cohort studies reporting on the association between levels of the 3 biomarkers of interest and key clinical outcomes. Retrospective cohort studies were excluded to be consistent with the approach taken for adults.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See sections 1.5.7 References – included studies (adults) and 1.5.8 References – included studies (babies, children and young people) for the full references of the included studies.

1.1.4.3 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion, are given in appendix J. These are reported separately for adults and for babies, children and young people.

1.2 Evidence for adults

1.2.1 Summary of studies included in the effectiveness and prognostic evidence

Table 2: Summary of studies included in the effectiveness evidence

Study details	Setting	Population	Intervention	Comparison	Outcomes	Risk of Bias	Comments
Randomised controlled trials (n = 4)							
Christ-Crain 2006 The ProCAP Study Switzerland	Hospital setting	Adult patients with CAP N = 302 Mean age = 70 years 60% were in PSI class IV or V 87% of patients had relevant comorbidities	PCT levels measured at admission and on days 4, 6 and 8. Antibiotics were discontinued on the basis of PCT cut-offs defined in the algorithm: - Discontinuation of antibiotics *strongly encouraged* when PCT <0.1 µg/L - Discontinuation of antibiotics *encouraged* when PCT between 0.1 µg/L and 0.25 µg/L - Continuation of antibiotics *encouraged* when PCT between 0.25 µg/L and 0.5 µg/L - Continuation of antibiotics *strongly encouraged* when PCT > 0.5 µg/L - In patients with very high PCT on admission (>10 µg/L), discontinuation of	Antibiotic treatment chosen on the basis of usual practice guidelines	Antibiotic duration Antibiotic prescription Clinical cure Mortality Treatment failure (composite of death, recurrence, relapse, persistence of CAP)	Low risk of bias	

Study details	Setting	Population	Intervention	Comparison	Outcomes	Risk of Bias	Comments
			antibiotics encouraged if levels decreased to less than 10% of the initial value (e.g., 1 µg/L instead of 0.25 µg/L).				
Gavazzi 2022 The PROPAGE Study France	Geriatric units	Elderly patients ≥ 80 years with a diagnosis of pneumonia N = 107 Mean age = 88 years 81% were in PSI class IV or V	PCT levels measured at admission and days 2, 4, 6 and 8. Intervention patients received an antibiotic regimen that was terminated early according to clinical algorithm guided by PCT levels: <u>Algorithm 1 (for use on Day 2)</u> - If PCT Day 0 and Day 2 < 0.25 ng/mL, stop antibiotics recommended - If PCT Day 0 and/or Day 2 > 0.25 ng/mL, continue antibiotics for 2 days then assess PCT at Day 4 (and apply algorithm 2) <u>Algorithm 2 (for use on Days 4, 6 and 8)</u> - If previous PCT value < 0.25 ng/mL, and patient is stable and has PCT < 0.1 ng/mL, *strongly recommend* stopping antibiotics - If previous PCT value < 0.25 ng/mL, and patient is stable and has PCT > 0.1 ng/mL and	Conventional antibiotic regimen that was terminated according to the treating physician's discretion and managed per usual treatment strategies according to the recommendations from the French Infectious Diseases Society (SPILF).	Antibiotic duration Recovery rate (physician judgement; no clinical sign pneumonia persisted) Mortality Adverse events (including death, hospitalisation, prolonging of existing hospitalisation, or events leading to permanent or significant disability/incapacity)	Moderate risk of bias	Baseline PCT levels were 2.6 (6.70) ng/ml in the PCT group and 4.8 (12.73) ng/ml in the control group. Although not significantly different, it does indicate a degree of difference in baseline PCT levels which may have impacted study findings. Downgraded for indirectness because the study population was narrow as it was ≥ 80 years, disabled, with poor nutritional status or at risk of malnutrition. Most of the population exhibited impaired cognitive function, declined functional status, high pneumonia severity scores, and respiratory

Study details	Setting	Population	Intervention	Comparison	Outcomes	Risk of Bias	Comments
			< 0.25 ng/mL, *recommend* stopping antibiotics - If previous PCT value > 0.25 ng/mL and < 10 ng/mL, and patient is stable and PCT < 0.25 ng/mL, *recommend* stopping antibiotics - If previous PCT value > 10 ng/mL, and patient is stable and PCT has decreased by >90%, *recommend* stopping antibiotics				decompensation upon presentation. 24/50 intervention patients did not comply with the PCT algorithm; reasons not provided. Per-protocol population included 26 PCT group patients.
Montassier 2019 France	Hospital EDs	Adult patients attending ED diagnosed with CAP N = 285 Median age = 67 years 40% were in PSI class IV or V	PCT levels measured at admission and on days 3, 5 and 7. Antibiotic discontinuation was recommended according to the PCT algorithm: - Discontinuation of antibiotics *strongly encouraged* when PCT <0.1 µg/L - Discontinuation of antibiotics *encouraged* when PCT between 0.1 µg/L and 0.25 µg/L - Continuation of antibiotics *encouraged* when PCT	After clinical evaluation, patients receiving a diagnosis of CAP were prescribed antibiotic treatment by the ED physician. On day 5, patients were re-evaluated using clinical stability criteria based on IDSA/ATS guidelines to	Antibiotic duration Proportion of patients treated with antibiotics for ≤5 days Clinical cure Overall adverse outcomes (composite of death from any cause, ICU admission for any reason, disease-specific	Moderate risk of bias	

Study details	Setting	Population	Intervention	Comparison	Outcomes	Risk of Bias	Comments
			between 0.25 µg/L and 0.5 µg/L - Continuation of antibiotics *strongly encouraged* when PCT > 0.5 µg/L Prespecified allowed exceptions to the procalcitonin algorithm included immediate need for ICU admission, respiratory or hemodynamic instability, and severe community-acquired pneumonia (Pneumonia Severity Index class IV or V).	stop antibiotic treatment. If the patient did not fulfil the stopping criteria, continuation of antibiotics was recommended for 2 more days, then the patient was re-evaluated.	complications, and recurrence of LRTI in need of antibiotics with or without hospital readmission)		
Schuetz 2009 The ProHOSP Trial Switzerland	Hospital EDs	Adult patients admitted with acute LRTI; results subgrouped for CAP. CAP population only – N = 925 Median age = 72.5	PCT levels measured at admission and on days 3, 5 and 7. PCT levels were communicated via a website to the treating physician, together with a treatment recommendation for antibiotics based on the PCT algorithm: - If PCT was less than 0.1 µg/L, continuation of antibiotics was *strongly discouraged*	Antibiotic use was in accordance with recommendations from up-to-date guidelines. In brief, antibiotic use was encouraged in CAP for 5 to 10 days in uncomplicated cases, at least 14 days in L pneumophila	Antibiotic duration Adverse effects of antibiotic treatment Length of hospital stay Overall adverse outcomes (composite of death from any cause, ICU admission for any reason, disease-specific	Low risk of bias	

Study details	Setting	Population	Intervention	Comparison	Outcomes	Risk of Bias	Comments
		71% were in PSI class IV or V	- If PCT was less than 0.25 µg/L, continuation of antibiotics was *discouraged* - If PCT was higher than 0.25 µg/L, continuation of antibiotics was *encouraged* - If PCT was higher than 0.5 µg/L, continuation of antibiotics was *strongly encouraged* - In patients with high PCT values on admission (> 10 µg/L), if PCT levels decreased by 80%, stopping antibiotics was *recommended*, and if PCT levels decreased by 90%, stopping antibiotics was *strongly recommended*. Overruling of the PCT algorithm was possible by prespecified criteria, namely in patients with immediate need for intensive care unit (ICU) admission, with respiratory or hemodynamic instability, or with positive antigen test for Legionella pneumophila.	CAP, at least 10 days in necrotizing CAP, and in the case of empyema or lung abscess, where drainage was suggested.	complications, and recurrence of LRTI in need of antibiotics with or without hospital readmission)		
Non-randomised cohort studies (n = 3)							
Akagi 2019	Hospital setting	Adult patients hospitalised with CAP	PCT levels measured at admission and on days 5 (+/-1 day), 8 (+/-1 day) and 11 (+/-1	For usual care in Japan, antibiotics are	Antibiotic duration	Moderate risk of bias	

Study details	Setting	Population	Intervention	Comparison	Outcomes	Risk of Bias	Comments
Japan	Prospective cohort: Oct 2014 to Dec 2017 Retrospective cohort: Oct 2010 to Sept 2014	(76%) or HCAP (24%) N = 232 Median age = 78 years 56% were in PSI class IV or V Admission PCT > 0.20 ng/mL (PCT group median = 0.76 ng/mL and control group median = 1.03 ng/mL)	day) and every 3 days thereafter if needed. Discontinuation of antibiotics was based on the following algorithm: - Discontinuation of antibiotics encouraged when PCT levels decreased to <0.20 ng/mL - Discontinuation of antibiotics strongly encouraged when PCT levels decreased to <0.10 ng/mL	discontinued when patients meet all (or all but one) of the following criteria: (1) body temperature <37.0°C, (2) normalization of WBC count, (3) improvement in CRP to less than 30% of peak levels and (4) apparent improvement of pneumonic shadows in chest X-ray images	Adverse event (recurrence of pneumonia during admission) Rehospitalisation due to pneumonia recurrence Mortality within 30 days		
Subedi 2020 United States	Intensive care units (ICU) Prospective cohort:	Adult patients admitted to ICU with a diagnosis of CAP (81%), HAP (15%) or VAP (4%)	Clinical pharmacists contacted the prescribing providers and requested an order for a baseline PCT level within 24 hours of initiating antibiotics and a repeat 24- to 48-hour PCT level. Based on the 2 serial PCT levels, clinical pharmacists made antibiotic	Usual care	Antibiotic duration Re-initiation of antibiotic therapy for initial infection within 72 hours of discontinuation	Moderate risk of bias	

Study details	Setting	Population	Intervention	Comparison	Outcomes	Risk of Bias	Comments
	Feb 2017 to July 2017 Retrospective cohort: Aug 2016 to Feb 2017	N = 74 Median age = 65.5 36% were on mechanical ventilation Baseline PCT median = 0.34 µg/L	recommendations as listed in the PCT algorithm. When making these recommendations, pharmacists had a collaborative discussion with the attending physician and accounted for patients' overall clinical status and objective data (e.g., microbiology results, WBC, bands, fevers, imaging). The choice of antibiotics and final decision with respect to continuing or discontinuing antibiotics was at the discretion of the attending physician. - If PCT is <0.1µg/L or reduces by >90%, cessation of antibiotics is *strongly encouraged* (but consider continuing antibiotics if patient is clinically unstable) - If PCT is 0.1-0.24µg/L or reduces by >80%, cessation of antibiotics is *encouraged* (but consider continuing antibiotics if patient is clinically unstable) - If PCT >= 0.25-0.5µg/L, cessation of antibiotics is *discouraged*		Length of hospital stay Length of ICU stay Incidence of *C. difficile* Mortality		

Study details	Setting	Population	Intervention	Comparison	Outcomes	Risk of Bias	Comments
			- If PCT is >0.5µg/L, cessation of antibiotics is *strongly discouraged.* - If PCT is >0.25µg/L and rising, or not decreasing by at least 10% per day, this is a poor prognostic indicator; consider expanding antibiotic coverage or other diagnoses.				
Townsend 2018 United States	Hospital settings; ward and ICU Prospective cohort: April 2017 to Nov 2017 Retrospective cohort: Nov 2016 to April 2017	Adult patients admitted via ED with LRTI; results subgrouped for CAP CAP population only – N = 255 Mean age = 63 22% had CURB-65 score of 3, 4 or 5	PCT levels measured on admission to ED and after 24 hours for patients admitted to ICU or 48 for patients admitted to the ward. PCT repeated every 48 hours for non-ICU patients and daily for ICU patients. PCT levels guided antibiotic discontinuation decisions: - If procalcitonin level < 0.1ug/L, bacterial infection highly unlikely, NO antibiotics! - If procalcitonin level 0.1-0.25ug/L, bacterial infection unlikely, no antibiotics. - If procalcitonin level 0.25-0.5ug/L, bacterial infection likely, antibiotics yes. - If procalcitonin level >0.5ug/L, bacterial infection /	Control patients were treated according to physician preference. Local treatment guidelines for pneumonia recommended antibiotic durations of 3–5 days for patients without immunocompromise or structural lung disease, 7 days with moderate immunocompromise or structural lung disease, and 10–14 days in	Antibiotic duration Length of hospital stay Overall adverse events (composite of new antibiotic prescription for LRTI, transfer to an ICU, death, antibiotic side effects, disease-specific complications (i.e., persistence or development of new pneumonia, lung abscess, empyema, or acute respiratory distress syndrome), and	Moderate risk of bias	The control period occurred during different parts of the calendar year, which may correspond to variations in antibiotic durations due to unmeasured factors such as the acquired experience among trainees and probability of admission based on fluctuating hospital volumes and seasonal variation in rates of respiratory illness.

Study details	Setting	Population	Intervention	Comparison	Outcomes	Risk of Bias	Comments
			sepsis highly likely, antibiotics YES! - If procalcitonin level decreases by 80-90% from the peak value, or drops below <0.25ug/L (non-ICU) or <0.5ug/L (ICU), consider stopping antibiotics. Overruling of the PCT algorithm was allowed for prespecified criteria, including respiratory or hemodynamic instability, life-threatening comorbidity, ICU admission, and severe illness.	patients with immunocompromise or poor initial response.	Clostridium difficile infection).		

ATS: American Thoracic Society; CAP: community acquired pneumonia; CRP: C-reactive protein; ED: emergency department; HAP: hospital acquired pneumonia; HCAP: healthcare associated pneumonia; ICU: intensive care unit; IDSA: Infectious Diseases Society; LRTI: lower respiratory tract infection; PCT: procalcitonin; PROPAGE: PROcalcitonine chez les Patients AGEs; PSI: pneumonia severity index; VAP: ventilator associated pneumonia; WBC: white blood cell

See appendix D for full evidence tables.

Table 3: Summary of studies included in the prognostic evidence – prospective cohort studies

Study details	Setting	Population	Number of patients	Prognostic factors	Outcomes predicted	Outcome rate in population, n (%)
Andrijevic 2014 Serbia	University hospital setting	Adult patients hospitalised with CAP	101	• Admission procalcitonin	Mortality within 30 days	25 (24.8%)

Study details	Setting	Population	Number of patients	Prognostic factors	Outcomes predicted	Outcome rate in population, n (%)
Chalmers 2008 Scotland, UK	Large teaching hospital	Adult patients hospitalised with CAP	570	• Admission C-reactive protein • Day 4 C-reactive protein	Mortality within 30 days Need for mechanical ventilation and/or inotropic support Development of complicated pneumonia (lung abscess, empyema, or complicated parapneumonic effusion)	55 (9.6%) 77 (13.5%) 42 (7.3%)
Coelho 2012 Brazil and Portugal	Intensive care units (ICU)	Adult patients admitted to ICU with severe CAP	191	• Admission C-reactive protein • Day 5 C-reactive protein • Day 7 C-reactive protein	Hospital mortality ICU mortality	47 (24.6%) 42 (21.9%)
Cornelis 2012 The Netherlands	Emergency department (ED) of a large teaching hospital	Adult patients hospitalised with CAP	395	• Admission C-reactive protein • Admission neutrophil to lymphocyte ratio	Mortality within 30 days ICU admission Duration of hospitalisation	23 (5.8%) 31 (7.8%) Mean (SD): 10.9 (11.7) days
Curbelo 2017 Spain	Hospital settings	Adult patients hospitalised with CAP	154	• Admission C-reactive protein • 72–120-hour C-reactive protein • Admission procalcitonin • 72–120-hour procalcitonin	Mortality within 30 days Mortality within 90 days	12 (7.79%) 20 (12.99%)

Study details	Setting	Population	Number of patients	Prognostic factors	Outcomes predicted	Outcome rate in population, n (%)
				• Admission neutrophil to lymphocyte ratio • 72–120-hour neutrophil to lymphocyte ratio		
El Maghraby 2020 Egypt	University hospital setting	Adult patients hospitalised with CAP	45	• Admission procalcitonin	Mortality within 30 days	20 (44%)
El-Dib 2015 Egypt	University hospital setting	Hospitalised patients with CAP	50	• Admission procalcitonin	CAP severity (severe CAP: requiring mechanical ventilation or vasopressor support for septic shock)	25 (50%)
Fernandes 2015 India	Pulmonary medicine wards	Hospitalised patients with CAP (≥15 years old)	55	• Admission procalcitonin	Mortality within 30 days	6 (10.9%)
Guo 2018 China	Hospital settings	Hospitalised patients with CAP	350	• Admission procalcitonin • Day 3 procalcitonin • Day 5 procalcitonin • Admission C-reactive protein • Day 3 C-reactive protein • Day 5 C-reactive protein	Mortality within 30 days	38 (10.86%)
Huang 2008	Emergency departments	Hospitalised patients with CAP	1651	• Admission procalcitonin	Mortality within 30 days	106 (6.4%)

Study details	Setting	Population	Number of patients	Prognostic factors	Outcomes predicted	Outcome rate in population, n (%)
United States						
Hur 2020 Turkey	Emergency departments	Hospitalised patients with CAP	123	• Admission procalcitonin • Admission C-reactive protein	Mortality within 30 days	34 (27.6%)
Kumar 2018 India	Unclear, but patients descried as critically ill so assume inpatient hospital settings	Critically ill patients with HAP	60	• Admission procalcitonin	In-hospital mortality	19 (32%)
Lacoma 2012 Spain	Emergency departments	ED patients with CAP	75	• Admission procalcitonin	Mortality (timescale unclear) ICU admission	6 (8%)
Naderi 2015 Iran	Hospital settings	Hospitalised patients with CAP	120	• Admission procalcitonin	Intensive vasopressor and respiratory support requirement In-hospital mortality	37 (30.8%) 28 (23.6%)
Park 2012 Korea	Emergency departments	ED patients with CAP	126	• Admission procalcitonin	Mortality within 28 days	16 (12.7%)
Siljan 2019 Norway	Hospital setting	Hospitalised patients with CAP	267	• Admission procalcitonin	Adverse outcome (admission to ICU or 30-day mortality)	51 (19%)
Surme 2020 Turkey	Hospital setting	Elderly patients hospitalised with CAP (79%) or HAP (21%)	184	• Admission procalcitonin • Admission C-reactive protein	Poor prognosis (septic shock, ICU admission, or death within 30 days)	55 (29.9%)

Study details	Setting	Population	Number of patients	Prognostic factors	Outcomes predicted	Outcome rate in population, n (%)
Travlos 2022 Greece	University hospital setting	Hospitalised patients with CAP	173	• Admission C-reactive protein	Mortality within 30 days	6 (3.47%)
Wang 2019 China	Hospital setting	Elderly patients hospitalised with CAP	214	• Admission procalcitonin • Admission C-reactive protein	Mortality within 30 days	82 (38.32%)
Wang 2020 China	Hospital setting	Hospitalised patients with severe pneumonia	148	• Admission procalcitonin • Admission C-reactive protein	Pneumonia severity (septic shock or need for ventilation) Mortality within 30 days (severe pneumonia group only)	74 (50%) 22/74 (29.7%)
Wang 2022 China	University hospital setting	Hospitalised patients with pneumonia	185	• Admission procalcitonin • Admission C-reactive protein • Admission neutrophil to lymphocyte ratio	CAP severity (septic shock or need for mechanical ventilation) Mortality within 90 days	72 (38.9%) 20 (10.8%)
Zhang 2023 China	Hospital setting	Hospitalised patients with severe pneumonia	152	• Admission procalcitonin • Admission C-reactive protein • Admission neutrophil to lymphocyte ratio	Mortality within 30 days	45 (29.6%)
Zhou 2018 China	Large University hospital	ED patients with CAP	226	• Admission procalcitonin	CAP severity (septic shock or need for mechanical ventilation) Mortality within 30 days	51 (22.6%) 39 (21.7%)

CAP: community acquired pneumonia; ED: emergency department; HAP: hospital acquired pneumonia; ICU: intensive care unit;

See appendix D for full evidence tables

1.2.2 Summary of the effectiveness and prognostic evidence for adults

1.2.2.1 Effectiveness evidence

1.2.2.1.1 Effectiveness of procalcitonin-guided antibiotic treatment

Table 4: GRADE Summary of findings table for procalcitonin-guided antibiotic de-escalation compared to usual care

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality of the evidence (GRADE)	Interpretation of effect
			Control	PCT-guided	Difference		
Duration of antibiotic therapy (days)	302 (1 RCT[1])	-	Mean 12.9 days	Mean 5.8 days	MD **7.1 lower** (8.44 lower to 5.76 lower)	⊕⊕⊕◯ Moderate[a]	Favours the intervention
Antibiotic use - antibiotics prescribed	1512 (3 RCTs[2])	**RR 0.90** (0.87 to 0.92)	99.2%	89.8%	**99 fewer per 1000** (79 fewer to 129 fewer)	⊕⊕⊕⊕ Moderate[b]	Favours the intervention
Antibiotic use day 5 to 6	1032 (2 RCTs[3])	**RR 0.64** (0.59 to 0.69)	91.6%	58.5%	**330 fewer per 1000** (284 fewer to 375 fewer)	⊕⊕⊕⊕ High	Favours the intervention
Antibiotic use day 7 to 8	1032 (2 RCTs[3])	**RR 0.52** (0.46 to 0.58)	77.0%	40.1%	**370 fewer per 1000** (323 fewer to 416 fewer)	⊕⊕⊕⊕ High	Favours the intervention
Antibiotic use after day 13	925 (1 RCT[4])	**RR 0.46** (0.32 to 0.64)	19.6%	8.9%	**106 fewer per 1000** (70 fewer to 133 fewer)	⊕⊕⊕◯ Moderate[a]	Favours the intervention

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality of the evidence (GRADE)	Interpretation of effect
			Control	PCT-guided	Difference		
New antibiotic prescription after hospitalisation	285 (1 RCT[5])	**RR 1.34** (0.72 to 2.52)	10.5%	14.1%	**36 more per 1000** (29 fewer to 159 more)	⊕◯◯◯ Very low[a,c,d]	Could not differentiate between interventions
New antibiotic prescription after hospitalisation	255 (1 non-RCT[6])	**RR 0.74** (0.34 to 1.62)	10.4%	7.7%	**27 fewer per 1000** (69 fewer to 64 more)	⊕◯◯◯ Very low[a,d,e]	Could not differentiate between interventions
Reinitiation of antibiotic therapy within 72 hours of discontinuation	74 (1 non-RCT[7])	**RR 1.00** (0.06 to 15.40)	2.7%	2.7%	**0 fewer per 1000** (25 fewer to 389 more)	⊕◯◯◯ Very low[a,d,e]	Could not differentiate between interventions
Pneumonia recurrence after antibiotic discontinuation	232 (1 non-RCT[8])	**RR 0.71** (0.23 to 2.19)	6.0%	4.3%	**18 fewer per 1000** (46 fewer to 72 more)	⊕◯◯◯ Very low[a,d,e]	Could not differentiate between interventions
Adverse effects from antibiotic treatment (including nausea, diarrhoea, and rash)	925 (1 RCT[4])	**RR 0.71** (0.57 to 0.87)	33.1%	23.5%	**96 fewer per 1000** (142 fewer to 43 fewer)	⊕⊕◯◯ Low[a,f]	Favours the intervention
Adverse effects from antibiotic treatment (including nausea, diarrhoea, and rash)	255 (1 non-RCT[6])	**RR 1.44** (0.42 to 4.99)	3.2%	4.6%	**14 more per 100** (19 fewer to 128 more)	⊕◯◯◯ Very low[a,d,e]	Could not differentiate between interventions
C. diff infection	329 (2 non-RCTs[9])	**RR 1.47** (0.25 to 8.66)	1.2%	1.8%	**6 more per 1000** (9 fewer to 95 more)	⊕◯◯◯ Very low[c,d]	Could not differentiate between interventions
Length of hospitalisation	302 (1 RCT[1])	-	Mean 12 days	Mean 13 days	MD **1 lower** (3.04 lower to 1.04 higher)	⊕⊕⊕◯ Moderate[a]	Could not differentiate between interventions

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality of the evidence (GRADE)	Interpretation of effect
			Control	PCT-guided	Difference		
Need for ICU admission	587 (2 RCTs[10])	**RR 1.19** (0.77 to 1.85)	10.9%	13.0%	**21 more per 1000** (25 fewer to 93 more)	⊕◯◯◯ Very low[c,d]	Could not differentiate between interventions
Need for ICU admission	255 (1 non-RCT[6])	**RR 1.20** (0.49 to 2.95)	6.4%	7.7%	**13 more per 1000** (33 fewer to 125 more)	⊕◯◯◯ Very low[a,d,e]	Could not differentiate between interventions
All-cause mortality	1619 (4 RCTs[11])	**RR 0.97** (0.67 to 1.39)	6.7%	6.5%	**2 fewer per 1000** (22 fewer to 26 more)	⊕⊕◯◯ Low[d]	Could not differentiate between interventions
All-cause mortality	561 (3 non-RCTs[12])	**RR 0.86** (0.34 to 2.19)	3.2%	2.8%	**5 fewer per 1000** (21 fewer to 39 more)	⊕◯◯◯ Very low[d,e]	Could not differentiate between interventions
Clinical cure	694 (3 RCTs[13])	**RR 1.00** (0.93 to 1.07)	81.8%	81.8%	**0 fewer per 1000** (57 fewer to 57 more)	⊕⊕⊕◯ Moderate[c]	Could not differentiate between interventions
Overall adverse outcome (composite measure)	1512 (3 RCTs[2])	**RR 0.81** (0.65 to 1.00)	19.8%	15.9%	**38 fewer per 1000** (69 fewer to 0 more)	⊕⊕⊕◯ Moderate[f]	Could not differentiate between interventions
Overall adverse outcome (composite measure)	255 (1 non-RCT[6])	**RR 0.96** (0.62 to 1.48)	24.8%	23.9%	**10 fewer per 1000** (94 fewer to 119 more)	⊕◯◯◯ Very low[a,d,e]	Could not differentiate between interventions

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **GRADE:** Grading of Recommendations, Assessment, Development, and Evaluations; **ICU:** intensive care unit; **MD:** mean difference; **OR:** odds ratio; **PCT:** procalcitonin; **RCT:** randomised controlled trial; **RR**: risk ratio

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality of the evidence (GRADE)	Interpretation of effect
			Control	PCT-guided	Difference		

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

a. Downgraded once for inconsistency: single study
b. Downgraded once as I^2 between 33.3% and 66.7% (I^2 = 40%)
c. Downgraded once as greater than 33.3% of the weight in the meta-analysis came from studies at moderate risk of bias
d. Downgraded twice as 95%CI crosses two clinical decision thresholds (0.8 and 1.25)
e. Downgraded twice: study at moderate risk of bias
f. Downgraded once as 95%CI crosses one clinical decision threshold (0.8)

[1] Christ-Crain 2006
[2] Christ-Crain 2006, Montassier 2019, Schuetz 2009
[3] Gavazzi 2022, Schuetz 2009
[4] Schuetz 2009
[5] Montassier 2019
[6] Townsend 2018
[7] Subedi 2020
[8] Akagi 2019
[9] Subedi 2020, Townsend 2018
[10] Christ-Crain 2006, Montassier 2019
[11] Christ-Crain 2006, Gavazzi 2022, Montassier 2019, Schuetz 2009
[12] Akagi 2019, Subedi 2020, Townsend 2018
[13] Christ-Crain 2006, Gavazzi 2022, Montassier 2019

1 See appendix F for full GRADE tables.

1.2.2.1.2 Summary of median and IQR data for procalcitonin-guided antibiotic de-escalation

Six studies reported median and IQR for antibiotic treatment duration and length of hospital stay. The data for these outcomes could not be pooled for meta-analysis so a summary of these findings is reported in Table 5 and Table 6. It is not possible to use GRADE to report the certainty of these outcomes, so the risk of bias for each trial is also reported in the tables.

Table 5: Antibiotic treatment duration for procalcitonin-guided antibiotic de-escalation

Study name and type	Procalcitonin group (median [IQR])	Control group (median [IQR])	Significance	Risk of Bias
Akagi 2019 Non-randomised control	8 days [7.5 to 11 days]	11 days [8 to 13 days]	$p < 0.001$[a]	Moderate
Gavazzi 2022 RCT	8 days [6 to 11 days]	10 days [8 to 12 days]	$p < 0.001$[b]	Moderate
Montassier 2019 RCT	10 days [7 to 15 days]	9 days [6 to 11 days]	p = 0.59, ns	Moderate
Schuetz 2009 RCT	7 days [4 to 10 days]	10 days [8 to 12 days]	Not reported	Low
Subedi 2020 Non-randomised control	6.3 days [4.4 to 8.6 days]	9.7 days [7.2 to 12 days]	$p < 0.001$	Moderate
Townsend 2018 Non-randomised control	6 days [4 days[c]]	7 days [3 days[c]]	$p = 0.045$	Moderate

IQR: interquartile range; ns: not significant; RCT: randomised controlled trial

Notes.

[a] Per protocol analysis

[b] ITT analysis. Results for per protocol analysis were PCT group 7 days (IQR: 6–10 days) vs. control group 10 days (IQR: 8–12); $p < 0.001$.

[c] Paper reports IQR as the range between the upper and lower quartile values.

Table 6: Length of hospital stay for procalcitonin-guided antibiotic de-escalation

Study name and type	Procalcitonin group (median [IQR])	Control group (median [IQR])	Significance	Risk of Bias
Montassier 2019 RCT	6 days [4 to 8.5 days]	5 days [3 to 8.5 days]	Not reported	Moderate
Schuetz 2009 RCT	8 days [5 to 13 days]	8 days [4 to 12 days]	$p > 0.05$, ns	Low

Study name and type	Procalcitonin group (median [IQR])	Control group (median [IQR])	Significance	Risk of Bias
Subedi 2020 – *length of hospital stay* Non-randomised control	8.2 days [6.4 to 20.9 days]	10.9 days [6.5 to 15.3 days]	*p* = 0.95, ns	Moderate
Subedi 2020 – *length of ICU stay* Non-randomised control	3.4 days [1.4 to 6.8 days]	2.8 days [1.8 to 6.3 days]	*p* = 0.88, ns	Moderate
Townsend 2018 Non-randomised control	3.5 days [4 days[a]]	3 days [3 days[a]]	*p* = 0.56, ns	Moderate

Notes.

[a] Paper reports IQR as the range between the upper and lower quartile values.

1.2.2.2 Prognostic evidence

1.2.2.2.1 C-reactive protein

Table 7: GRADE Summary of findings table for C-reactive protein

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality of the evidence (GRADE)	Interpretation of effect
			Survivors	Non-survivors	Difference		
Admission CRP for survivors vs non-survivors (mortality within 30 days)	1421 (7 studies[1])	-	-	-	MD 18.28 **lower** (30.69 lower to 5.88 lower)	⊕◯◯◯ Very low[1]	Favours lower admission CRP
Admission CRP for survivors vs non-survivors (mortality within 90 days)	154 (1 study[2])	-	-	-	MD 14 **lower** (50.9 lower to 22.9 higher)	⊕◯◯◯ Very low[2,3,8]	Could not differentiate
Day 3 CRP for survivors vs non-survivors (mortality within 30 days)	504 (2 studies[3])	-	-	-	MD 44.39 **lower** (69.38 lower to 19.39 lower)	⊕◯◯◯ Very low[4,9]	Favours lower day 3 CRP
Day 3 CRP for survivors vs non-survivors (mortality within 90 days)	154 (1 study[2])	-	-	-	MD 32 **lower** (55.81 lower to 8.19 lower)	⊕◯◯◯ Very low[2,5,8]	Favours lower day 3 CRP
Day 5 CRP for survivors vs non-survivors (mortality within 30 days)	523 (2 studies[4])	-	-	-	MD 67.38 **lower** (97.67 lower to 37.1 lower)	⊕◯◯◯ Very low[6]	Favours lower day 5 CRP
Day 7 CRP for survivors vs non-survivors (mortality within 30 days)	173 (1 study[5])	-	-	-	MD 82 **lower** (168.07 lower to 4.07 higher)	⊕◯◯◯ Very low[2,7]	Could not differentiate

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality of the evidence (GRADE)	Interpretation of effect
			Survivors	Non-survivors	Difference		
Admission CRP and illness severity (severe vs non severe CAP)	148 (1 study[6])	-	-	-	MD 62.55 **lower** (66.32 lower to 58.78 lower)	⊕◯◯◯ Very low[2]	Favours lower admission CRP
Day 4 CRP decrease by ≥50% vs Day 4 CRP increase or decrease by <50% (mortality within 30 days)	268 (1 study[7])	**RR 0.03** (0 to 0.23)	0.57%	18.3%	**177 fewer per 1000** (141 fewer to 183 fewer)	⊕◯◯◯ Very low[2]	Favours day 4 CRP decrease by ≥50%
Day 4 CRP decrease by ≥50% vs Day 4 CRP increase or decrease by <50% (need for invasive ventilation or inotropic support)	268 (1 study[7])	**RR 0.08** (0.02 to 0.25)	1.7%	22.6%	**208 fewer per 1000** (from 169 fewer to 221 fewer)	⊕◯◯◯ Very low[2]	Favours day 4 CRP decrease by ≥50%
Day 4 CRP decrease by ≥50% vs Day 4 CRP increase or decrease by <50% (development of complications)	268 (1 study[7])	**RR 0.12** (0.04 to 0.34)	2.3%	19.4%	**170 fewer per 1000** (from 128 fewer to 186 fewer)	⊕◯◯◯ Very low[2]	Favours day 4 CRP decrease by ≥50%

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CRP:** C-reactive protein; **GRADE:** Grading of Recommendations, Assessment, Development, and Evaluations; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality of the evidence (GRADE)	Interpretation of effect
			Survivors	Non-survivors	Difference		

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded once as I2 was between 33.3% and 66.7% (I2 = 49%)
[2] Downgraded once - single study
[3] Downgraded once as 95%CI crosses one calculated MID (35.7)
[4] Downgraded once as 95% CI crosses one calculated MID (58.6)
[5] Downgraded once as 95%CI crosses one calculated MID (25)
[6] Downgraded once as 95%CI crosses one calculated MID (57.9)
[7] Downgraded once as 95%CI crosses one calculated MID (53.5)
[8] Downgraded once as study rated as moderate risk of bias (no baseline sample characteristics reported)
[9] Downgraded once as >33.3% of the weight in the meta-analyses came from a study at moderate risk of bias (no baseline sample characteristics reported)

1 Cornelis 2012, Curbelo 2017, Guo 2018, Hur 2020, Travlos 2022, Wang 2020, Zhang 2023
2 Curbelo 2017
3 Curbelo 2017, Guo 2018
4 Guo 2018, Travlos 2022
5 Travlos 2022
6 Wang 2020 (1)
7 Chalmers 2008 (1)

1

Table 8: Mortality by C-reactive protein response patterns

Coelho (2012) grouped patients into 3 response groups based on the trajectory of CRP over time and reported mortality rates across CRP response groups. The groups were defined as:

- Fast response: Day 5 CRP is less than 40% of Day 1 CRP
- Slow response: Day 5 CRP is more than 40% of Day 1 CRP and Day 7 CRP is less than 80% of Day 1 CRP
- Non-response: Day 7 CRP is more than 80% of Day 1 CRP

Outcome	Fast response	Slow response	Non-response
Hospital mortality	9.5%	25.9%	43.2%
ICU mortality	4.6%	17.3%	36.4%

Table 9: Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for C-reactive protein

Study	Cut-off (mg/L)	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
Mortality within 30 days					
Wang 2022	43.1	93.33	43.65	1.66	0.15
Wang 2019	78.62	73.64	68.45	2.33	0.39
Chalmers 2008	100	96.3	34.5	1.47	0.11
Hur 2020	179	58.8	77.5	2.61	0.53
Development of pneumonia related complications					
Chalmers 2008	100	97.6	33.8	1.47	0.07
Adverse outcome (septic shock, admission to ICU or 30-day mortality)					
Surme 2020	79	79	52	1.65	0.4
Need for invasive ventilation or inotropic / vasopressor support					
Wang 2022	39.5	86.44	56.1	1.97	0.24
Chalmers 2008	100	94.8	35.7	1.47	0.15

Note. All positive LRs and negative LRs calculated by NICE analyst.

1.2.2.2.2 Procalcitonin

Table 10: GRADE Summary of findings table for Procalcitonin (PCT)

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality of the evidence (GRADE)	Interpretation of effect
			Survivors	Non-survivors	Difference		
Admission PCT for survivors vs non-survivors (mortality within 30 days)	1114 (9 studies[1])	-	-	-	MD 3.52 **lower** (5.77 lower to 1.26 lower)	⊕◯◯◯ Very low[1,2]	Favours lower admission PCT
Admission PCT for survivors vs non-survivors (mortality within 90 days)	154 (1 study[2])	-	-	-	MD 6 **lower** (13.6 lower to 1.6 higher)	⊕◯◯◯ Very low[3,4]	Could not differentiate
Day 3 PCT for survivors vs non-survivors (mortality within 30 days)	504 (2 studies[3])	-	-	-	MD 1.7 **lower** (3.11 lower to 0.29 lower)	⊕⊕◯◯ Low	Favours lower day 3 PCT
Day 3 PCT for survivors vs non-survivors (mortality within 90 days)	154 (1 study[2])	-	-	-	MD 1.1 **lower** (2.04 lower to 0.16 lower)	⊕◯◯◯ Very low[3,5]	Favours lower day 3 PCT
Day 5 PCT for survivors vs non-survivors (mortality within 30 days)	350 (1 study[4])	-	-	-	MD 3.50 **lower** (6.47 lower to 0.53 lower)	⊕◯◯◯ Very low[3,6]	Favours lower day 5 PCT
In-hospital mortality for admission PCT negative (≤0.5ng/ml) vs PCT positive (>0.5ng/ml) patients	60 (1 study[5])	**RR 0.27** (0.11 to 0.66)	14.7%	53.8%	**393 fewer for 1000** (from 183 fewer to 479 fewer)	⊕◯◯◯ Very low[3]	Favours PCT negative (≤0.5ng/ml)
Admission PCT and illness severity (severe vs non severe CAP)	198 (2 studies[6])	-	-	-	MD 1.04 **higher** (0.96 higher to 1.12 higher	⊕⊕◯◯ Low	Favours lower admission PCT

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality of the evidence (GRADE)	Interpretation of effect
			Survivors	Non-survivors	Difference		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CAP: community-acquired pneumonia**; CI:** confidence interval; **GRADE:** Grading of Recommendations, Assessment, Development, and Evaluations; **MD:** mean difference; **OR:** odds ratio; **PCT:** procalcitonin; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded twice as I2 was greater than 66.7% (I2 = 98%)
[2] Downgraded once as 95%CI crosses one calculated MID (4.44)
[3] Downgraded once – single study
[4] Downgraded once as 95%CI crosses one calculated MID (8.65)
[5] Downgraded once as 95%CI crosses one calculated MID (1.05)
[6] Downgraded once as 95%CI crosses one calculated MID (4.65)

1 Andrijevic 2014, Curbelo 2017, El Maghraby 2020, Fernandes 2015, Guo 2018, Hur 2020, Kumar 2018, Wang 2020, Zhang 2023
2 Curbelo 2017
3 Curbelo 2017, Guo 2018
4 Guo 2018
5 Kumar 2018
6 El-Dib 2015 (1), Wang 2020

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Table 11: Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for Procalcitonin

Study	Cut-off (ng/ml)	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
Mortality within 30 days					
Huang 2008	0.1	92	35	1.42	0.23
Lacoma 2012	0.115	83.3	50	1.67	0.33
Wang 2022	0.195	95	59.75	2.36	0.08
Kumar 2018	0.285	78.9	34.1	1.2	0.62
Park 2012	0.35	68.75	92.73	9.46	0.34
Hur 2020	0.9	76.4	62.9	2.06	0.38
Lacoma 2012	1.03	50	77.9	2.26	0.64
Zhou 2018	1.16	76.3	85.7	5.34	0.28
Fernandes 2015	2.0	100	73.47	3.77	0
Naderi 2015	2.0	50	75	2	0.67
Andrijevic 2014	2.56	76	61.8	1.99	0.39
Wang 2019	2.96	74.51	82.02	4.14	0.31
Development of pneumonia related complications requiring ICU admission					
Lacoma 2012	0.115	85.7	50.7	1.74	0.28
Lacoma 2012	1.03	57.1	79.1	2.73	0.54
Adverse outcome (septic shock, admission to ICU or 30-day mortality)					
Siljan 2019	0.91	72	58	1.71	0.48
Surme 2020	0.295	83	69	2.68	0.25
Zhou 2018	1.16	90.2	78.3	4.16	0.13
Need for invasive ventilation or inotropic / vasopressor support					
Naderi 2015	2	81.3	61.1	2.09	0.31
Wang 2022	0.25	70.42	77.78	3.17	0.38

Note. All positive LRs and negative LRs calculated by NICE analyst.

1.2.2.2.3 Neutrophil-lymphocyte ratio

Table 12: GRADE Summary of findings table for Neutrophil-lymphocyte ratio (NLR)

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality of the evidence (GRADE)	Interpretation of effect
			Survivors	Non-survivors	Difference		
Admission NLR for survivors vs non-survivors (mortality within 30 days)	701 (3 studies)	-	-	-	MD 5.45 **lower** (9.53 lower to 1.37 lower)	⊕◯◯◯ Very low[1,2]	Favours lower admission NLR
Admission NLR for survivors vs non-survivors (mortality within 90 days)	154 (1 study)	-	-	-	MD 3.5 **lower** (7.59 lower to 0.59 higher)	⊕◯◯◯ Very low[3,4]	Could not differentiate
Day 3-5 NLR for survivors vs non-survivors (mortality within 30 days)	154 (1 study)	-	-	-	MD 12.5 **lower** (19.78 lower to 5.22 lower)	⊕◯◯◯ Very low[3,5]	Favours lower day 3-5 NLR
Day 3-5 NLR for survivors vs non-survivors (mortality within 90 days)	154 (1 study)	-	-	-	MD 10.4 **lower** (15.65 lower to 5.15 lower)	⊕◯◯◯ Very low[3,6]	Favours lower day 3-5 NLR
Admission NLR < 10 or ≥ 10 – ICU admission	395 (1 study)	**RR 0.41** (0.19 to 0.87)	4.57%	11.1%	**66 fewer per 1000** (from 14 fewer to 90 fewer)	⊕◯◯◯ Very low[3,7]	Favours admission NLR < 10
Admission NLR < 10 or ≥ 10 – in-hospital mortality	395 (1 study)	**RR 0.28** (0.11 to 0.74)	2.54%	9.09%	**65 fewer per 1000** (from 24 fewer to 81 fewer)	⊕◯◯◯ Very low[3]	Favours admission NLR < 10
Admission NLR in patients hospitalised for < 10 days or ≥ 10 days	346 (1 study)	-	-	-	MD 4.50 **lower** (7.73 lower to 1.27 lower)	⊕◯◯◯ Very low[3,8]	Favours lower admission NLR

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality of the evidence (GRADE)	Interpretation of effect
			Survivors	Non-survivors	Difference		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **GRADE:** Grading of Recommendations, Assessment, Development, and Evaluations; **ICU:** intensive care unit; **MD:** mean difference; **NLR**: Neutrophil-lymphocyte ratio **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded once as I2 was between 33.3% and 66.7% (I2 = 63%)
[2] Downgraded once as 95%CI crosses one calculated MID (4.71)
[3] Downgraded once – single study
[4] Downgraded once as 95%CI crosses one calculated MID (4.2)
[5] Downgraded once as 95%CI crosses one calculated MID (6.4)
[6] Downgraded once as 95%CI crosses one calculated MID (5.95)
[7] Downgraded once as 95%CI crosses one clinical MID (0.8)
[8] Downgraded once as 95% CI crosses one calculated (7.7)

1

Table 13: Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for Neutrophil-lymphocyte ratio

Study	Cut-off	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
Mortality within 30 days					
Curbelo 2017	10	63.6	65	1.82	0.56
Mortality within 90 days					
Wang 2022	12	95	84.76	6.23	0.06
Need for mechanical ventilation or vasopressor support					
Wang 2022	9.7	68.49	94.59	12.66	0.33

Note. All positive LRs and negative LRs calculated by NICE analyst.

1.3 Evidence for babies, children and young people

1.3.1 Summary of studies included in the effectiveness and prognostic evidence

Table 14: Summary of studies included in the effectiveness evidence

Study details	Setting	Population	Intervention	Comparison	Outcomes	Risk of Bias
Baer 2013 RCT Switzerland	Emergency departments of two paediatric hospitals	Children and adolescents aged >1 month to < 18 years presenting to ED with LRTI (subgroup for CAP). N = 337 (full LRTI sample); N = 215 CAP only subgroup Median age = 2.7 years (IQR 1.1 to 5.2 years)	Antibiotics were initiated, continued or terminated on the basis of PCT cut-offs previously used in trials for adults. The algorithm provides PCT based decision categories for the likelihood of requiring antibiotic treatment for bacterial LRTI: - definitely (>0.5 µg/L) - probably (0.26–0.5 µg/L) - probably not (0.1–0.25 µg/L) - definitely not (<0.1 µg/L) For all patients, discontinuation of antibiotics was encouraged upon clinical stabilization and when PCT values fell below 0.25µg/L; or for patients with initial PCT values >10 µg/L, when levels decreased below 90% of the initial value. The PCT algorithm could be overruled for patients with life threatening infections, defined as severe co-morbidity, emerging ICU need during initial follow-up, or hemodynamic or respiratory instability.	Clinically guided standard care: antibiotic treatment was initiated based on physician assessment and clinical guidelines for a duration of 7–10 days for uncomplicated CAP and 14 or more days for complicated CAP, e.g., parapneumonic effusions, empyema, abscess.	Antibiotic duration Antibiotic prescription Antibiotic side effects Duration of hospitalisation Occurrence of complications, serious adverse events or disease-specific failure[a]	Moderate risk of bias

Study details	Setting	Population	Intervention	Comparison	Outcomes	Risk of Bias
Esposito 2011 RCT Milan	Paediatric hospital setting	Children aged > 1 month and < 14 years diagnosed with CAP. N = 310 Mean age = 4.31; SD = 3.76 years.	• Antibiotics were not administered to the children with admission PCT levels of <0.25 ng/mL, but were immediately given in the case of higher values. • The untreated children were given antibiotics only if their PCT levels increased to ≥0.25 ng/mL, and continued the therapy until the levels had returned to this value. • The children who received antibiotics from the time of admission were treated until their PCT levels were <0.25 ng/mL, and resumed antibiotics only if their PCT levels subsequently increased to more than this value. • All patients were clinically reassessed every day during hospitalisation. Untreated children showing no reduction in the clinical signs and symptoms of disease after three days could be treated with antibiotics regardless of their PCT levels. • In the case of severe clinical deterioration and regardless of their PCT levels, the children	Children in the control group were treated in accordance with the Italian Society of Paediatrics (SIP) guidelines: antibiotic monotherapy chosen on the basis of age if mild; combined beta-lactam and macrolide therapy if severe. The duration of administration in the control group was that recommended by the SIP (i.e. 7-14 days depending on disease severity).	Duration of hospitalisation Antibiotic side effects Adverse event: recurrence of respiratory symptoms New antibiotic prescription (resumed after discontinuation)	Moderate risk of bias

Study details	Setting	Population	Intervention	Comparison	Outcomes	Risk of Bias
			could be treated with antibiotics (if previously untreated) or their treatment could be modified on the basis of their paediatrician's judgment.			

CAP: community-acquired pneumonia; ED: emergency department; ICU: intensive care unit; IQR: interquartile range; LRTI: lower respiratory tract infection; PCT: procalcitonin; RCT: randomised controlled trial; SD: standard deviation

[a] Composite measure defined as follows: Occurrence of complications (e.g., parapneumonic effusions, empyema, lung abscess, necrotising pneumonitis, ARDS) or serious adverse events (e.g., hospital readmission, admission to ICU, unexpected life threatening condition, death), or disease specific failure (e.g., recurrent infection in need of antibiotics, or development of any co-morbid condition requiring antibiotics irrespective of primary LRTI diagnosis, worsening of condition, new onset of respiratory distress)

Table 15: Summary of studies included in the prognostic evidence

Study details	Setting	Population	Number of patients	Prognostic factors	Outcomes predicted	Outcome rate in population, n (%)
Florin 2020 CARPE DIEM Study USA	ED of a children's hospital	Children aged 3 months to 18 years presenting to ED with suspected CAP. Mean age 5.6 years (SD 4.6 years)	477	• Admission procalcitonin • Admission C-reactive protein	ICU admission Adverse event: development of severe sepsis or septic shock Need for positive-pressure ventilation	42 (8.8%) 10 (2.1%) 19 (4%)
Golubeva 2021 Russia	Hospital setting	Children aged 2–18 years with acute pneumonia; 51 (30.9 %) children	165	• Admission C-reactive protein • Day 3 C-reactive protein	CAP severity: - Acute pneumonia	 82 (49.7%) 32 (19.4%)

Study details	Setting	Population	Number of patients	Prognostic factors	Outcomes predicted	Outcome rate in population, n (%)
		had acute necrotising pneumonia.		• Day 14 C-reactive protein	- Progression of illness or lack of response to treatment Adverse event: Development of necrotising pneumonia	51 (30.9%)
Song 2022 China	Hospital setting	Children diagnosed with CAP	150	• Admission procalcitonin • Admission C-reactive protein • Admission Neutrophil to lymphocyte ratio	CAP severity: - Mild/moderate - Severe	 75 (50%) 75 (50%)

CAP: community-acquired pneumonia; ED: emergency department; ICU: intensive care unit; SD: standard deviation

1.3.2 Summary of the effectiveness and prognostic evidence for babies, children and young people

1.3.2.1 Effectiveness evidence

Table 16: GRADE Summary of findings table for procalcitonin-guided antibiotic de-escalation compared to usual care for babies, children and young people

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	Interpretation of effect
			Control	PCT-guided	Difference		
Antibiotic prescription	215 (1 RCT)	**RR 0.92** (0.79 to 1.08)	77.6%	71.4%	**62 fewer per 1000** (163 fewer to 62 more)	⊕◯◯◯ Very low[a,b,c,h]	Could not differentiate
Antibiotic side effects	525 (2 RCTs)	**RR 0.53** (0.40 to 0.71)	34.4%	18.2%	**161 fewer per 1000** (206 fewer to 100 fewer)	⊕◯◯◯ Very low[d,e,i]	Favours PCT group
New antibiotic prescription (resumed after discontinuation)	313 (1 RCT)	**RR 0.34** (0.05 to 2.11)	2.5%	0.9%	**17 fewer per 1000** (24 fewer to 28 more)	⊕◯◯◯ Very low[b,f,g]	Could not differentiate
Duration of hospitalisation	310 (1 RCT)	-	-	-	MD **0.92 lower** (1.42 lower to 0.41 lower)	⊕⊕◯◯ Low[a,b]	Favours PCT group
Occurrence of complications, serious adverse events or disease-specific failure	215 (1 RCT)	**RR 1.14** (0.67 to 1.95)	18.7%	21.3%	**26 more per 1000** (62 fewer to 178 more)	⊕◯◯◯ Very low[a,b,g,h]	Could not differentiate
Adverse event: recurrence of respiratory symptoms	307 (1 RCT)	**RR 0.23** (0.04 to 1.36)	3.9%	0.9%	**30 fewer per 1000** (37 fewer to 14 more)	⊕◯◯◯ Very low[b,f,g]	Could not differentiate

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	Interpretation of effect
			Control	PCT-guided	Difference		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **GRADE:** Grading of Recommendations, Assessment, Development, and Evaluations; **MD:** mean difference; **PCT:** procalcitonin; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

a. Downgraded once due to moderate risk of bias (outcome measurement relied on self-assessment and patient/caregiver diary entries)
b. Downgraded once - single study
c. Downgraded once as 95%CI crosses one clinical decision threshold (0.8)
d. Downgraded once as greater than 33.3% of the weight in the meta-analysis came from studies at moderate risk of bias
e. Downgraded twice as I2 was greater than 66.7% (I2 = 87%)
f. Downgraded once due to moderate risk of bias (trial not registered)
g. Downgraded twice as 95%CI crosses two clinical decision thresholds (0.8 and 1.25)
h Downgraded once as study was partially applicable (only 48% of children here hospitalised)
I Downgraded once as >33.3% of the weight in the meta-analysis came from a study rated as partially applicable

1.3.2.2 Prognostic evidence

Table 17: GRADE summary of findings table for admission biomarkers by CAP severity

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk	Risk with biomarkers				
Admission CRP by CAP severity		MD **41.52 higher** (34.05 higher to 48.99 higher)	-	150 (1 non-randomised study)	⨁◯◯◯ Very low[a,b]	Favours lower admission CRP
Admission Procalcitonin by CAP severity		MD **72.32 higher** (58.07 higher to 86.57 higher)	-	150 (1 non-randomised study)	⨁◯◯◯ Very low[a,b]	Favours lower admission PCT
Admission Neutrophil to lymphocyte ratio by CAP severity		MD **13.98 higher** (11.37 higher to 16.59 higher)	-	150 (1 non-randomised study)	⨁◯◯◯ Very low[a,b]	Favours lower admission NLR

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CAP: community acquired pneumonia**; CI:** confidence interval; **CRP:** C-reactive protein; **GRADE:** Grading of Recommendations, Assessment, Development, and Evaluations; **MD:** mean difference; **NLR:** Neutrophil-lymphocyte ratio; **PCT:** procalcitonin

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

a. Downgraded once for moderate risk of bias - no information on inclusion criteria for age; states only 'children'

1 b. Downgraded once - single study

Table 18: Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for C-reactive protein

Study	Cut-off (mg/L)	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
Severe versus non-severe CAP					
Florin 2020	3.3	54	57	1.26	0.8
ICU admission					
Florin 2020	2.35	58	46	1.07	0.91
Need for invasive ventilation					
Florin 2020	3.47	59	58	1.4	0.71
Development of severe sepsis or septic shock					
Florin 2020	3.74	75	61	1.92	0.41

Note. All positive LRs and negative LRs calculated by NICE analyst.

Table 19: Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for Procalcitonin

Study	Cut-off (ng/ml)	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
Severe versus non-severe CAP					
Florin 2020	0.35	48	59	1.17	0.88
ICU admission					
Florin 2020	0.16	66	41	1.12	0.83
Need for invasive ventilation					
Florin 2020	0.23	63	48	1.21	0.77
Development of severe sepsis or septic shock					
Florin 2020	0.8	64	74	2.46	0.49

Note. All positive LRs and negative LRs calculated by NICE analyst.

1.4 Economic evidence

1.4.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update. See Appendix B – Literature search strategies **Error! Reference source not found.**for the search strategy.

This search retrieved 3,201 studies. Based on title and abstract screening, 3,168 of the studies could confidently be excluded for this question. Thirty-three studies were excluded following the full-text review. Leaving no included studies for this review question. See **Error! Reference source not found.**for the study selection process.

1.4.2 Excluded studies

See **Error! Reference source not found.**for a list of excluded studies, with reason for exclusion.

1.4.3 Summary of included economic evidence

There are no included studies in this review question.

1.4.4 Economic model

No original economic modelling was completed for this review question.

1.4.5 Unit costs

No unit costs were supplied for this review question.

1.5 The committee's discussion and interpretation of the evidence

1.5.1 The outcomes that matter most

The committee agreed that for the evidence on the use of procalcitonin for discontinuing antibiotics, the main outcome of interest was duration of antibiotic use because the length of antibiotic courses and the proportion of people being given antibiotics are important in relation to antibiotic stewardship and resistance. Outcomes relating to patient safety were important for understanding the clinical impact of discontinuing antibiotic treatment, so the committee agreed that mortality, need for ICU admission and other indicators of illness severity such as need for invasive mechanical ventilation or vasopressor support were very important for decision making. They agreed that these outcomes were also important for the prospective cohort evidence on biomarkers and prognosis, to understand how admission biomarker levels and their trajectory over time may influence pneumonia severity and survival.

In the effectiveness evidence on PCT-based antibiotic use, it was noted that the protocol listed antibiotic type and duration only as primary outcomes. Some additional outcomes relating to antibiotic use were also extracted because they provided important information on wider indicators of antibiotic use, which is important for considering broader issues relating to antimicrobial stewardship, and the effectiveness of the PCT algorithm for informing stopping decisions. These included reinitiation of antibiotics after discontinuation and antibiotic prescription after hospitalisation. Outcomes relating to recurrence of pneumonia or respiratory symptoms after antibiotic discontinuation were considered to qualify as adverse events.

1.5.2 The quality of the evidence

The effectiveness evidence was limited to the use of procalcitonin (PCT) for discontinuing antibiotics in both adults and in babies, children and young people. There was no evidence linking biomarkers to other aspects of de-escalating care such as discharge from ICU or discharge home, so the committee were unable to make any recommendations about these aspects of care for patients with pneumonia. In the absence of further randomised trial evidence, the committee considered evidence from prospective cohort studies demonstrating the association between biomarker levels and pneumonia prognosis, which gave them information from which they were able to make inferences about potential care decisions informed by biomarker levels.

The evidence on PCT for discontinuing antibiotics in adults was based on 7 studies (4 RCTs and 3 non-randomised studies) assessed to be at either low or moderate risk of bias, generating outcomes that were rated between high and very low confidence. It was noted that confounders were not considered in the non-randomised study evidence, so a greater amount of focus was placed on the RCT evidence for decision making. Several outcomes relating to antibiotic use were classed as high or moderate confidence, while outcomes relating to clinical outcomes such as need for ICU admission, all-cause mortality and clinical cure were rated as low or very low confidence. The main reasons for downgrading were

inconsistency due to a predominance of single study outcomes, and imprecision, where outcomes showed very wide confidence intervals and a lot of uncertainty around the effect estimate. The evidence on PCT for discontinuing antibiotics in babies, children and young people was based on 2 studies assessed to be at moderate risk of bias, generating outcomes that were all rated as very low confidence, mainly because they were based on a single study or because of wide confidence intervals that reflected uncertainty in the effect.

The committee reflected on the quality of the studies and noted that many of them showed much longer durations of antibiotic treatment than would currently be recommended in UK practice. They highlighted that current NICE guidance for pneumonia is 5-day antibiotic treatment duration and suggested that it would be unusual to give more than 7 days antibiotic treatment for an uncomplicated pneumonia, so the control group durations of 10 to 12 days were of concern as they were not directly relevant to current practice. They noted that none of the trials were conducted in the UK and considered that the longer antibiotic durations used in the included studies may have been standard practice in non-UK settings when the trials were conducted, so they had concerns about the applicability of this evidence. This was particularly true for the 2 studies of children and young people because both trials were conducted over 10 years ago. They agreed that the evidence demonstrated a reduction in antibiotic durations when patients were receiving a 10-12 day course, but there was no evidence to show that PCT can be used to reduce durations from the 5 days standard duration currently used in the UK.

Other concerns about the quality of the evidence were noted. Several trials reported C-reactive protein (CRP) levels as well as PCT so the committee was concerned that clinicians in these trials may have had access to CRP measurements as well as PCT, which may have informed their decision about discontinuing antibiotic treatment. The committee also expressed concern about the funding source of several of the larger Swiss trials of adults (The ProCAP study and the ProHOSP trial) as these were funded by companies who manufacture PCT tests.

Prognostic evidence from the prospective cohort studies was largely good quality and directly applicable but was rated as moderate risk of bias due to the observational nature of the study designs. Similarly, these studies started as low certainty in GRADE, so all outcomes in the prognostic evidence were rated as low or very low confidence.

1.5.3 Benefits and harms

The committee agreed that using procalcitonin to inform decisions about antibiotic continuation or discontinuation for patients with CAP can reduce antibiotic exposure by reducing the duration of antibiotic courses without causing any significant difference in illness-related outcomes such as pneumonia recurrence, re-hospitalisation, ICU admission or mortality. However, the committee recognised that the reduction in antibiotic duration from approximately 12 days to approximately 6 days for adults, and from approximately 9 days to approximately 6 days for children, was not relevant to UK practice where 5-day antibiotic courses are recommended standard care. The committee agreed that without any UK-based evidence to test the efficacy of using PCT to reduce antibiotic treatment under 5 days they were unable to make any specific recommendations about PCT-guided antibiotic treatment for either adults or babies, children and young people.

The committee noted that PCT-guided antibiotic treatment reduced the duration of hospital stay from 6 days to 5 days for children and young people hospitalised with pneumonia. They considered this an important outcome, particularly in terms of health economics because the cost of repeat PCT testing is significantly lower than the cost of 1 day hospital admission. However, this finding was from a single study (separated into mild and severe CAP subgroups) and was rated as very low confidence, so the committee did not consider this evidence sufficient or that they had enough confidence in it to be able to make any recommendations about this. Furthermore, the committee agreed that the duration of hospitalisation for children with non-complicated pneumonia in the UK is often very short, and referred to data from the British Thoracic Society's national paediatric pneumonia audit in 2016/17 which showed a median length of stay for CAP of 1 day. Because of this, they agreed that the benefit of reducing hospital stay by 1 day from 6 days to 5 days, as reported in this study, is unlikely to be applicable to a UK population. They also noted that there can be numerous other reasons that influence discharge home for children, including feeding issues or dehydration.

The committee agreed that the prognostic evidence showed there is a link between the level of inflammatory response, measured by the 3 biomarkers under review, and key clinical outcomes. They considered the sensitivity and specificity data and agreed that there was no clear cut-off or threshold value for any of the biomarkers, but overall, the body of evidence suggested that elevated biomarker levels were associated with poor prognosis, as shown by outcomes such as need for ICU admission, pneumonia severity, development of pneumonia-related complications, development of sepsis, and mortality. They agreed that elevated biomarkers could be used to identify patients at risk of more severe illness or deterioration. They also noted that low levels of these biomarkers could help to rule out complications or poor prognosis and agreed that they could be used to identify patients at lower risk when their biomarker levels are in the normal range.

The committee noted that the biomarkers appear to be of most use when measured at baseline or admission, potentially because follow-up measurements may be influenced by treatments received, so they agreed that clinicians should aim to assess biomarker levels early in the patients' care pathway. This is in line with the existing recommendation to assess CRP on admission to hospital for adults, although they acknowledged that admission CRP testing is not required for children because it is an invasive test and does not necessarily influence treatment decisions.

There was limited data on the trajectory of the biomarkers over time, with most studies reporting absolute values at various follow-up points rather than change in biomarker levels. The small number of studies that reported on this in adults appeared to show that decreasing levels of CRP from day 1 to day 4 was associated with better prognosis than CRP levels that either increase or remain elevated. The committee agreed that this is in line with their clinical experience, where a halving of CRP over 3 days is often used as a rule of thumb to indicate a patients' improving clinical condition. Likewise, a failure to halve is indicative of treatment failure or a need for further investigations and consideration of potential complications. This pattern was also seen for PCT.

The committee noted that the algorithms for PCT-guided antibiotic treatment included additional stopping thresholds of an 80% or 90% reduction in PCT for patients with very high

PCT values on admission (>10ng/mL), as well as providing absolute values for stopping. They agreed that clinicians should consider relative biomarker levels and their change over time, as well as absolute values. For this reason, the committee made a recommendation to assess CRP and PCT 3-4 days after starting treatment in patients where there is a concern about treatment failure, and another recommendation about high inflammatory marker levels that do not improve being indicative of treatment failure, but they decided not to suggest any absolute values or thresholds in the recommendation because there were no clear thresholds in the evidence and the relative reduction may be more informative than the absolute value. They agreed that patients whose CRP or PCT levels do not significantly improve with treatment are likely to need review by a senior clinician. The committee agreed that it would not be necessary to assess CRP or PCT on day 3 or 4 in patients who are responding well to treatment, so they didn't recommend that these tests should be done routinely for all patients.

The committee considered the relative performance of each of the 3 biomarkers and recognised that although all 3 showed a similar pattern of findings in the prognostic evidence, there were no direct comparisons to establish whether they were equivalent or whether 1 was better able to predict prognosis. They outlined that CRP is routinely used on admission to assess adult patients presenting with suspected pneumonia, and in most hospitals, this would be considered standard care. The committee agreed that PCT is generally equivalent to CRP, but they noted that not all hospitals have access to routine PCT testing and it is generally slightly more expensive than CRP. Nevertheless, they acknowledged that use of PCT is increasing and referred to evidence from the PEACH study (Procalcitonin Evaluation of Antibiotic Use in COVID-19 Hospitalised Patients) that demonstrated approximately 80% of hospitals are now using PCT routinely. PCT is also better able to influence antibiotic decision making through established algorithms for discontinuation, as seen in the RCT evidence of this review. However, overall, the committee concluded that there is not enough good quality evidence to support a formal switch from the routine use of CRP to the routine use of PCT on admission for patients with pneumonia. They agreed that, due to their apparent equivalence, clinicians could use their judgement when deciding which biomarker to use, but that this did not need to be specified in a recommendation, so they referred to both CRP and PCT. They considered the evidence for NLR and agreed that although it showed a similar pattern of results to CRP and PCT, there was comparatively less evidence for this biomarker of the 3 reviewed and not enough evidence to support a recommendation to use NLR over existing standard care. The committee also noted that not all clinicians are familiar with this biomarker and it is not yet routinely used, although it could be calculated from a full blood count which is routinely taken.

1.5.4 Cost effectiveness and resource use

There was no existing cost-effectiveness evidence for this review question for adults or babies, children and young people. The committee were aware that CRP is currently commonly used. The committee noted that the CRP unit costs vary across the country but generally are low (£10 and under). The committee expressed the view that PCT is less widely used however, the PEACH study found that 84% of hospitals use it routinely. According to the committee, the PCT test is only slightly more expensive than CRP test at about £14.

The committee explained that using CRP or PCT can reduce the length of antibiotic treatment. For example, if the CRP or PCT has decreased enough, clinicians can be confident in stopping the antibiotics after 5 days. This will potentially reduce antibiotic usage, which will support the reduction in anti-microbial resistance. Currently there is no agreed way to quantify the benefits of the reduction in anti-microbial resistance however, the benefit could potentially be substantial. Antibiotic costs are low; therefore, reducing the length of treatment using either CRP or PCT is unlikely to be cost saving as the cost of a few days of antibiotics is not more than the cost of a CRP or PCT test. However, there are significant other benefits that support overall antibiotic stewardship. For example, the clinical effectiveness review found that PCT reduced antibiotic duration and prescriptions, antibiotic use at various time points, including discharge, and reduced antibiotic-related adverse events. Therefore, the committee was of a view that PCT would be very likely cost effective when considering these and also broader benefits associated with antibiotic stewardship.

These recommendations are for a subset of people with pneumonia who are admitted to a hospital. Therefore, given that these tests are already used and that only the smaller subset of people with pneumonia will be affected, these recommendations are unlikely to result in a substantially increased number of tests. This means that the impact on resource use resulting from these recommendations is unlikely to be significant.

1.5.5 Other factors the committee took into account

The committee discussed issues relating to antibiotic stewardship. They agreed that biomarkers show some promise as an approach to reducing antibiotic use but agreed that a large element of reducing antibiotic use involves clinician behaviour. They reflected on the many different attempts that have been made to reduce antibiotic use for suspected respiratory tract infections, including longstanding recommendations for 5-day courses in the community but agreed that overall, antibiotic prescribing rates remain high, although work is ongoing in this area. The committee discussed concerns about the number of people prescribed second antibiotic courses for acute cough. The committee were concerned that introducing biomarker testing would just result in more tests, more costs, and still not impact on behaviour change, so they were reluctant to recommend repeated testing, particularly without strong evidence that it is effective. Nevertheless, the committee agreed that biomarkers may be used alongside clinician judgement to give clinicians the confidence to make decisions about reducing antibiotic dose, duration or route of administration. The committee also agreed that the expectations of patients can also be a factor in decisions about antibiotic use, and that clear explanations should be given to patients about why they may not get the antibiotics they were expecting, or why they may have a shortened course.

1.5.6 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.1, 1.10.7 and 1.10.8.

1.5.7 References – included studies (adults)

1.5.7.1 Effectiveness

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Travlos, Apostolos, Bakakos, Agamemnon, Vlachos, Konstantinos F et al. (2022) C-Reactive Protein as a Predictor of Survival and Length of Hospital Stay in Community-Acquired Pneumonia. Journal of personalized medicine 12(10)

Wang, Fei, Yang, Shuo, Liu, Chong et al. (2022) Matrix Metalloproteinase 3: a Novel Effective Biomarker for Predicting the Mortality and the Severity of Pneumonia. Clinical laboratory 68(1)

Wang, J Gao, YY Zhu, J Huang, YM Li, W (2020) Serum procalcitonin levels in predicting the prognosis of severe pneumonia patients and its correlation with white blood cell count and C-reactive protein levels. INTERNATIONAL JOURNAL OF CLINICAL AND EXPERIMENTAL MEDICINE 13(2): 809 - 815

Wang, Yanhui, Zhang, Shan, Li, Liang et al. (2019) The usefulness of serum procalcitonin, C-reactive protein, soluble triggering receptor expressed on myeloid cells 1 and Clinical Pulmonary Infection Score for evaluation of severity and prognosis of community-acquired pneumonia in elderly patients. Archives of gerontology and geriatrics 80: 53-57

Zhang, C.; Zheng, F.; Wu, X. (2023) Predictive value of C-reactive protein-to-albumin ratio for risk of 28-day mortality in patients with severe pneumonia. Journal of Laboratory Medicine 47(3): 115-120

Zhou, Haijiang, Guo, Shubin, Lan, Tianfei et al. (2018) Risk stratification and prediction value of procalcitonin and clinical severity scores for community-acquired pneumonia in ED. The American journal of emergency medicine 36(12): 2155-2160

1.5.8 References – included studies (babies, children and young people)

1.5.8.1 Effectiveness

Baer, Gurli, Baumann, Philipp, Buettcher, Michael et al. (2013) Procalcitonin guidance to reduce antibiotic treatment of lower respiratory tract infection in children and adolescents (ProPAED): a randomized controlled trial. PloS one 8(8): e68419

Esposito, Susanna, Tagliabue, Claudia, Picciolli, Irene et al. (2011) Procalcitonin measurements for guiding antibiotic treatment in pediatric pneumonia. Respiratory medicine 105(12): 1939-45

1.5.8.2 Prognostic

Florin, Todd A, Ambroggio, Lilliam, Brokamp, Cole et al. (2020) Biomarkers and Disease Severity in Children With Community-Acquired Pneumonia. Pediatrics 145(6)

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Appendices

Appendix A – Review protocols

Review protocol for biomarkers to de-escalate care

ID	Field	Content
1.	Review title	In people in hospital with a diagnosis of community- or hospital-acquired pneumonia, what is the clinical and cost effectiveness of monitoring C-reactive protein or procalcitonin and other biomarkers (or combinations of biomarkers) in addition to clinical observation in helping to determine when to deescalate or change treatment and when to change the place of care (for example, from ICU to non-ICU care or discharge from hospital)?
2.	Review question	In people in hospital with a diagnosis of community- or hospital-acquired pneumonia, what is the clinical and cost effectiveness of monitoring C-reactive protein or procalcitonin and other biomarkers (or combinations of biomarkers) in addition to clinical observation in helping to determine when to deescalate or change treatment and when to change the place of care (for example, from ICU to non-ICU care or discharge from hospital)?
3.	Objective	The aim of this review is to evaluate the effectiveness of CRP, procalcitonin, or other biomarkers in patients hospitalised with pneumonia for guiding patient management and de-escalating care, such as determining whether it is safe or appropriate stop or change antibiotic treatment, and whether to discharge from hospital.

4.	Searches	**Overall approach** The searches will comprise the following elements: • a combined search for cost effectiveness evidence covering all review questions in this guideline. • a combined search for systematic reviews covering all review questions in this guideline. • searches for effectiveness evidence specific to this review question, which will be further divided into a search relating to adults and a search covering children and young people. **Searches for cost effectiveness evidence** A combined search will be undertaken to cover the cost effectiveness aspects of all the review questions in a single search. The following databases will be searched for the cost effectiveness evidence: • Econlit via Ovid • Embase via Ovid • International HTA database via INAHTA website • MEDLINE ALL via Ovid The sensitive version of the validated NICE cost utility filter will be applied to the MEDLINE and Embase search strategies (Hubbard et al., 2022 [doi: 10.1186/s12874-022-01796-2]). Searches for cost effectiveness evidence will be limited to 2014-current (the searches for NICE guideline CG191 were completed in March 2014). The MEDLINE and Embase searches will be limited to evidence from Organisation for Economic Co-operation and Development (OECD) member states using the validated NICE filter (Ayiku et al., 2021 [doi: 10.5195/jmla.2021.1224]).

		Effectiveness evidence: combined search for systematic reviews The search for systematic reviews relating to all review questions in this guideline will cover reviews published since the searches for NICE guideline CG191 were completed in March 2014. The sources for this will be: • Cochrane Database of Systematic Reviews (CDSR) via Wiley • Epistemonikos via https://www.epistemonikos.org/ This is the standard NICE practice agreed by the Guidelines Methods Group in September 2022 for identifying systematic reviews for routine guideline searches. **Effectiveness evidence: searches specific to this review question** The searches for effectiveness evidence specific to this review question will use the following databases: • Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley • Embase via Ovid • MEDLINE ALL via Ovid The principal search strategy will be developed in MEDLINE and then adapted, as appropriate, for use in the other sources listed, taking into account their size, search functionality and subject coverage. To ensure potentially relevant records are not missed the following will be checked as required: • The reference lists of any appropriate studies • Later citations of any key trials, reviews, studies or protocols. The seed references for these actions will be identified from the search for systematic reviews, the scoping searches for this guideline, or the evidence reviews for previous NICE guidelines.

		The guideline committee or other stakeholders could also be asked if they are aware of any other potentially relevant studies that could be considered. The searches will be split into a strategy covering adults and a separate strategy covering children and young people. The searches relating to adults will be conducted from March 2014. The searches relating to children will not have a date limit. Both searches will apply appropriate validated study filters for randomised controlled trials and prognostic studies. **Managing all search results** Database functionality will be used, where available, to exclude from all searches: • Animal studies • Conference abstracts and posters • Editorials, letters, news items and commentaries • Registry entries for ongoing clinical trials or those that contain no results • Theses and dissertations • Papers not published in the English language With the agreement of the guideline committee, the searches will be re-run 6-8 weeks before final submission of the review and further studies retrieved for inclusion. The information services team at NICE will quality assure the principal search strategy and peer review the other strategies. Any revisions or additional steps will be agreed by the review team before being implemented. The full search strategies for all databases will be published in the final review.

5.	Condition or domain being studied	Community acquired pneumonia. Hospital acquired pneumonia.
6.	Population	**Inclusion:** Babies over 28 days (corrected gestational age), children, young people (age <18 years) and adults (≥18 years) with pneumonia (community or hospital acquired) requiring management in hospital. • CAP is defined as pneumonia that is acquired outside hospital • HAP is defined as pneumonia that occurs 48 hours or more after admission to hospital and is not incubating at hospital admission, or within 10 days of a previous hospital admission for a different problem. Note: studies that include a broader population (e.g., sepsis) will be included if: (a) they give results stratified for pneumonia; or (b) ≥ 75% patients have pneumonia. **Exclusion:** • Babies up to and including 28 days (corrected gestational age). • People with COVID-19 pneumonia. • People who acquire pneumonia while intubated (ventilator-associated pneumonia). • People who are severely immune-compromised (have a primary immune deficiency or secondary immune deficiency related to HIV infection, or severe drug or systemic disease-induced immunosuppression, for example, people who have taken immunosuppressant cancer therapy or undergone organ transplantation).

		• People in whom pneumonia is an expected terminal event. • People with non-pneumonic infective exacerbations of bronchiectasis. • People with non-pneumonic infective exacerbations of chronic obstructive pulmonary disease. • People with pneumonia associated with cystic fibrosis. • People with aspiration pneumonia as a result of inhaling a large bolus of gastric contents.
7.	Intervention	Usual care (clinical observation) plus biomarkers of interest: • C-reactive protein • Procalcitonin • Neutrophil/lymphocyte ratio Will include serial measurements or single test after initial admission assessment. CRP tests may be comparing results on e,g. day 3 to day 1, whereas PCT may be tested daily. Absolute values and change-from-baseline values included. All thresholds investigated will be reported to aid identification of the optimum cut-off. Threshold definitions will be according to study protocols – but differences will be noted. Focus is on use of these biomarkers to stop / change / deescalate care in patients already diagnosed and hospitalised with pneumonia; not to inform diagnosis or decision to admit to hospital / initiate antibiotics.
8.	Comparator	Usual care (clinical observation)

9.	Types of study to be included	**For the effectiveness evidence:** Systematic reviews of RCTs and RCTs Non-randomised controlled trials **For the prognostic evidence** Prospective cohort studies Retrospective cohort studies if insufficient prospective cohort studies. We will use a stepwise approach, so if insufficient prospective studies (e.g., <5 good quality, directly relevant papers) then we will look at retrospective; but retrospective will be excluded if we identify enough prospective studies.
10.	Other exclusion criteria	
11.	Context	Patients with community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) who are admitted to hospital are currently monitored by routine physiological observations, repeat clinical assessments and blood tests. Evidence of improvement in the patient's condition informs decisions about when to stop antibiotic therapy and when to discharge from hospital. Absence of improvement or deterioration guides change in empirical antibiotic therapy. Currently this approach is unstructured, with the potential for over or under treatment with antibiotics and inappropriate discharge decisions. A more objective assessment using biomarkers such as CRP and procalcitonin may be better than clinical observations and judgement alone when making decisions about managing patients with pneumonia (e.g., stopping antibiotics, discharging patients).

12.	Primary outcomes (critical outcomes)	• Mortality within 30 days • Antibiotic type (broad or narrow spectrum) and duration • ICU admission • Need for invasive ventilation • Length of hospital stay • Length of ICU stay • Hospital re-admission within 30 days For RCTs and non-randomised control trials, we will report outcome data for intervention and control groups. For prospective cohort studies in the prognostic part of the review, we will use HRs, ORs and RRs. Where reported we will include • Sens/spec • LR+/- • AUC. Sens/spec will be converted to LR
13.	Secondary outcomes (important outcomes)	• HRQoL (measured using validated tools such as the EQ5D or SF-36; or using condition-specific measures of QoL such as the CAP Symptom Questionnaire or the St George's Respiratory Questionnaire) • Adverse events / treatment harms • Hospital acquired infections, including C. diff rates

14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. Any disagreements will be resolved by discussion with other members of the technical review team. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For SRs, the ROBIS (Risk of Bias in Systematic Reviews) checklist will be used. For RCTs, the Cochrane risk of bias (RoB) 2 tool will be used. For observational studies, the Cochrane ROBINS-I tool will be the preferred tool. The CASP cohort study checklist will be used if ROBINS-I is not appropriate. For prospective studies, we will use the QUIPS checklist.
16.	Strategy for data synthesis	Where possible, meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions.

		Where data can be disambiguated it will be separated into the subgroups identified in section 17 (below). Continuous outcomes will be analysed as mean differences, unless multiple scales are used to measure the same factor. In these cases, standardised mean differences will be used instead. Pooled relative risks will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Absolute risks will be presented where possible. Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be deemed to be inappropriate if one or both of the following conditions is met: Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. In any meta-analyses where some (but not all) of the data comes from studies at high risk of bias, a sensitivity analysis will be conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses will be reported. Similarly, in any meta-analyses where some (but not all) of the data comes from indirect studies, a sensitivity analysis will be conducted, excluding those studies from the analysis.

		GRADE will be used to assess the quality of the outcomes. All outcomes in this review will be rated as high quality initially and downgraded from this point. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically (visually) assess the potential for publication bias. Minimally important differences (MIDs) will be discussed with the committee and if established MIDs are not identified, default MIDs will be used. These are 0.80 and 1.25 for dichotomous outcomes, and 0.5 times the control group SD for continuous outcomes.
17.	Analysis of sub-groups	The following groups will be considered separately if data are available: • CAP and HAP • Age: 0-1; 1-5; 5-18; Adults • CAP severity measured by PSI or CURB-65 • Antibiotic therapy before admission • Corticosteroid therapy • Site of care – ICU and non-ICU
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☒ Prognostic ☐ Qualitative ☐ Epidemiologic

		☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	TBC		
22.	Anticipated completion date	TBC		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐

		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** Guideline Development Team B, Centre for Guidelines, NICE. **5b Named contact e-mail** pneumoniadev@nice.org.uk **5c Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	From the Guideline Development Team: • Chris Carmona, Technical Adviser • Hannah Stockton, Technical Analyst • Michellie Young, Technical analyst		

		• Steph Armstrong, Senior Health Economist • Eric Slade, Health Economic Adviser • Paul Levay, Information Specialist • Christine Harris, Project Manager • Adam O'Keefe, Project Manager
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Project information | Pneumonia: diagnosis and management (update) | Guidance | NICE
29.	Other registration details	

30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Community acquired pneumonia, hospital acquired pneumonia, biomarkers, CRP, procalcitonin, patient management, antibiotic treatment, discharge, ICU.
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published

		☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	
36.	Details of final publication	www.nice.org.uk

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Appendix B – Literature search strategies

Background and development

Overall approach

Each evidence review for this guideline has a search conducted in three parts:

- Part 1: Systematic review searches

A single search for all systematic reviews relating to pneumonia published from 2014-current was done separately in November 2023 and re-run in October 2024. The results were screened for relevance to all the review questions. The potentially relevant results from this search were also used to create the seed references for reference list checking and forward citation searching for the effectiveness and prognostic evidence searches.

- Part 2: Effectiveness and prognostic evidence searches

This search was developed separately and tailored to each evidence review. The searches for effectiveness and prognostic evidence (Part 2) were run on 23 February 2024.For this review, it was further divided into two parts: 2A (covering adults since March 2014); and 2B (children and young people with no date limits). The results of these searches were screened separately.

- Part 3: Cost effectiveness searches

A single search covering the cost effectiveness elements of all review questions was done separately in November 2023 and re-run in October 2024. This was a top-level search for all cost utility studies published from 2014-current.

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for each part.

This search report is based on the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategies below were quality assured (QA) by a trained NICE SIS. All translated search strategies were peer reviewed by another SIS to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

All search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Search limits, restrictions and filters

Formats

Limits were applied in adherence to standard NICE practice (as set out in the Identifying the evidence chapter of the manual) and the eligibility criteria listed in the review protocol to exclude:

- Animal studies
- Case reports
- Conference abstracts and posters
- Editorials, letters, news items and commentaries
- References not published in the English language
- Registry entries for ongoing clinical trials or those that contain no results
- Theses and dissertations.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

> Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

For the Cost Effectiveness (Part 3) searches, the validated NICE OECD filters were used in MEDLINE and Embase to remove records about countries that are not members of the Organisation for Economic Co-operation and Development (OECD), in line with the search protocol. The filters were used without amendment. The filters are not available for the other databases used. The OECD filters were not applied to the Systematic Review (Part 1) or Effectiveness (Part 2) searches.

> Ayiku L et al. (2021) The NICE OECD countries' geographic search filters: Part 2 - Validation of the MEDLINE and Embase (Ovid) filters. *Journal of the Medical Library Association*, 109(4), 583–589.

Date limits

A date limit of 2014-current was applied to the Systematic Review (Part 1) and Cost Effectiveness (Part 3) searches. This date limit was used because the searches for NICE CG191 Pneumonia in adults: diagnosis and management (published in December 2014) were last run on 17 March 2014.

The Effectiveness searches (Part 2) were limited as follows:

- Part 2A: 1 March 2014 onwards as this was an update of CG191.
- Part 2B: no date limit as this population had not been considered previously.

Study-type filters

The Systematic Review (Part 1) searches had no filters, as the content for CDSR and Epistemonikos is pre-filtered.

The Effectiveness searches for Part 2 used RCT and prognostic study filters, in line with the protocol.

The standard RCT filters in use at NICE were applied. The MEDLINE RCT filter was McMaster Therapy – Medline – "best balance of sensitivity and specificity" version. The standard NICE modifications were used: the MeSH heading randomized controlled trial/ (equivalent to randomized controlled trial.pt) was exploded to capture newer, narrower terms; and the free-text term randomized.mp was changed to randomi?ed.mp. to capture both UK and US spellings.

> Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

> Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association*, 94(1), 41-47.

The Prognostic Study Filter was the current version of the NGA filter that was used in the CG191 searches (last updated 17/11/21). The filter was amended with the addition of MeSH and Emtree terms for Prognosis, which testing showed would increase recall of potentially relevant papers, although it is acknowledged that this also affected the precision.

Cost effectiveness searches

In line with the protocol, the validated NICE Cost Utility Filter was used in the MEDLINE and Embase searches for Cost Effectiveness (Part 3). The sensitive version of the filter was selected and it was used without amendment. Subject coverage in the Econlit, International HTA Database and NHS EED databases is already pre-specified and so it is not appropriate to apply filters in them.

> Hubbard W et al. (2022) Development and validation of paired MEDLINE and Embase search filters for cost-utility studies. *BMC Medical Research Methodology*, 22(1), 310.

Key decisions

Part 1: Systematic review searches

This search was conducted according to the standard NICE practice since the "Proposal to limit systematic review (SR) searching for routine guideline searches" was accepted by the NICE Guideline Methods Group (GMG) in September 2022. This process means that only sources which aggregate systematic reviews are searched in addition to the Cochrane Database of Systematic Reviews. The methods used to aggregate reviews for Epistemonikos are sufficiently sensitive with higher precision (Rada et al., 2020) compared to using standard Boolean search filters in general medical databases (Lee et al., 2012). Testing during scoping showed that other aggregators of systematic reviews, such as the Campbell Collaboration, Dopher and Health Evidence, would not be relevant for inclusion in this protocol.

Lee E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

Rada G et al. (2020) Epistemonikos: a comprehensive database of systematic reviews for health decision-making. *BMC Medical Research Methodology*, 20, 286.

Parts 1-3: Pneumonia terms

The same set of pneumonia terms was developed in November 2023 to use in all evidence reviews for this guideline. These terms aimed to cover all the included populations named in the final scope (section 3.1), namely babies over 28 days (corrected gestational age), children, young people and adults with suspected or diagnosed community-acquired or hospital acquired pneumonia.

A set containing 183 items was created to test the comprehensiveness of the searches. The 183 records were derived from the papers included in CG191 and the papers included in the 10 most recent Cochrane reviews about pneumonia.

The search terms built on the search strategies developed for NICE CG191 Pneumonia in adults and two antibiotic prescribing guidelines (NG138 and NG139).

The CG191 searches had a line to NOT out the MeSH term "pneumonia, ventilator-associated". This was not retained in the search as it was inadvertently excluding relevant papers that discussed several types of pneumonia (e.g., see PMIDs 29722052 or 32822880 or 28655326 or 34823043).

The CG191 searches truncated the free text to pneumoni* but this was amended following clinical advice that pneumonia is a form of pneumonitis but not all pneumonitis is pneumonia.

The CG191 searches had an additional line describing chest infection. It was not necessary to retain this line in order to retrieve any of the 183 items in the test set and so it was removed, which reduced the population search by around 41,000 results in MEDLINE.

The previous strategies could not be used directly because of changes to Medical Subject Headings (MeSH) since 2019. Using the previous searches would now retrieve all MEDLINE results about COVID-19, as well as pneumonia. It is now

necessary to choose individual MeSH headings from the hierarchy. The choice of headings was made in conjunction with the technical team in the scoping searches in October 2023. Headings for Aspiration, Lipid, Enzootic and Swine Pneumonia, as well as Pneumocystis and COVID-19 were not included. This approach reduced the number of results with just the population terms from 340,000 with the CG191 approach to 124,000. None of the test set were lost by adopting this approach.

Seven options were then tested to optimise the precision of the pneumonia free-text terms. The options tested the feasibility of excluding free-text terms for aspects known to be out of scope (such as COVID-19 or ventilator-associated pneumonia). None of the options made a sufficient difference to the volume to justify making the strategies much more complicated and risk missing relevant papers (the most plausible option only reduced the entire pneumonia literature from 227,500 to 225,900 results). The option to add further free text to define the relevant types of pneumonia (such as bacterial pneumonia) was rejected as it risked missing relevant papers because some abstracts just referred to treating pneumonia, without specifying which type or subtype it was.

At the committee meeting GCOMM1 on 20 December 2023 feedback was received from the committee that rickettsial and cryptogenic organizing pneumonia were not relevant to the UK context and could safely be removed from the search strategies. These terms feature in the Part 1 systematic review and Part 3 cost effectiveness searches as these were completed before the meeting (and were retained in the re-runs for consistency).

The same approach to subject headings was applied in Embase, although the COVID-19 headings are not part of the pneumonia hierarchy in Emtree. The following headings from the pneumonia hierarchy were not chosen: Acute chest syndrome, Acute lupus pneumonitis, Allergic pneumonitis, Aspiration pneumonia, Chemical pneumonitis, Enzootic pneumonia, Eosinophilic pneumonia, Loeffler pneumonia, Experimental pneumonia, Lung infiltrate, Pneumonic effusion, Radiation pneumonia, Parasitic pneumonia, Pneumocystis pneumonia, Pulmonary candidiasis, Pulmonary toxoplasmosis, Legionnaire disease, Pulmonary actinomycosis, Ventilator associated pneumonia, Ventilator associated bacterial pneumonia, Checkpoint inhibitor pneumonitis, and Severe acute respiratory syndrome. Searches after 20/12/23 also excluded Rickettsial pneumonia and Bronchiolitis obliterans organizing pneumonia.

The same free-text terms developed initially in MEDLINE were used in Embase.

Part 2: Effectiveness and prognostic evidence searches

The strategies are in the structure:

Part 2A: Pneumonia AND (CRP OR ProCT OR NLR) AND (Settings OR Treatment decisions OR Relevant outcomes) AND (RCTs OR Prognostics) AND Limits AND 2014-Current

Part 2B: Pneumonia AND (CRP OR ProCT OR NLR) AND (Settings OR Treatment decisions OR Relevant outcomes) AND (Children OR Young People) AND (RCTs OR Prognostics) AND Limits

The search results for Part 2 were screened in two separate EPPI-Reviewer files because adults had already been covered in CG191. The terms for pneumonia, the interventions and study-type filters were identical in both searches. The date limits

were adjusted, with Part 2A limited to March 2014 onwards and Part 2B having no date limits.

As the searches for Part 2A do not have any age-related terms, there is some overlap with the search results for Part 2B. This was not problematic as the results were being screened separately. The search terms for children and young people in Part 2B were adapted from a previous search for this guideline (Corticosteroids for treating pneumonia in children search Part 2C).

The search covers the three biomarkers requested at the committee meeting GCOMM2 on 13 February 2024 (CRP, Procalcitonin, NLR). CRP and Procalcitonin for adults were included in CG191. NLR was not covered in CG191 but the technical team decided that the evidence before 2014 did not need to be included.

The protocol covers treatment decisions for people diagnosed with pneumonia in secondary care. The search includes a set of terms for settings, treatment decisions and relevant outcomes. A test set of 26 papers, including 20 for adults and 6 for children, was created from results of the search for systematic reviews, the scoping searches and the included papers in CG191. All 26 were retrieved by the terms for pneumonia and the three biomarkers. The search terms for settings, treatments and outcomes retrieves 22 of the 26 although on closer examination the four missed papers were diagnostic studies that would not be relevant to this protocol. All six relevant papers were retrieved by the terms for children and young people.

The MeSH term "Procalcitonin" was introduced in 2019, and so "Calcitonin" was included. This doesn’t apply in Embase as the "Procalcitonin" Emtree term was added in 1976.

The Emtree terms for the three biomarkers were all focussed. This reduced the test search from 4004 to 2573. A sample of the papers that would be missed was reviewed and none were relevant to this protocol.

Part 1: Systematic review searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	20/11/2023	Wiley	Cochrane Database of Systematic Reviews Issue 11 of 12, November 2023	177
Epistemonikos	20/11/2023	Epistemonikos	Version available on 20/11/23	2096

Re-run results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	15/10/2024	Wiley	Cochrane Database of Systematic Reviews Issue 10 of 12, October 2024	8
Epistemonikos	15/10/2024	Epistemonikos	Version available on 15/10/2024	2571

Search strategy history

Database name: Cochrane Database of Systematic Reviews (CDSR)

Searches
#1 [mh ^pneumonia] or [mh ^bronchopneumonia] or [mh ^pleuropneumonia] or [mh ^"pneumonia, bacterial"] or [mh ^"chlamydial pneumonia"] or [mh ^"pneumonia, mycoplasma"] or [mh ^"pneumonia, pneumococcal"] or [mh ^"pneumonia, rickettsial"] or [mh ^"pneumonia, staphylococcal"] or [mh ^"pneumonia, necrotizing"] or [mh ^"pneumonia, viral"] or [mh ^"organizing pneumonia"] or [mh ^"cryptogenic organizing pneumonia"] or [mh ^"healthcare-associated pneumonia"] 5252
#2 (pneumonia or pneumonias or bronchopneumon* or pleuropneumon*):ti,ab 15137
#3 #1 or #2 16754
#4 #1 or #2 in Cochrane Reviews 244
#5 #1 or #2 with Cochrane Library publication date Between Jan 2014 and Nov 2023, in Cochrane Reviews 177
Note: in the re-run Line #5 was changed to #1 or #2 with Cochrane Library publication date Between Nov 2023 and Oct 2024, in Cochrane Reviews.

Database name: Epistemonikos

Searches
These are the lines as they were input into the interface for the re-run:
1 title:(bronchopneumonia* OR pleuropneumonia* OR broncho-pneumonia OR pleuro-pneumonia or broncho-pneumonias OR pleuro-pneumonias OR "broncho pneumonia" OR "pleuro pneumonia" or "broncho pneumonias" OR "pleuro pneumonias")
2 abstract:(bronchopneumonia* OR pleuropneumonia* OR broncho-pneumonia OR pleuro-pneumonia or broncho-pneumonias OR pleuro-pneumonias OR "broncho pneumonia" OR "pleuro pneumonia" or "broncho pneumonias" OR "pleuro pneumonias")
3 title:(pneumonia OR pneumonias)
4 abstract:((pneumonia OR pneumonias) AND (HAP OR nosocomial* OR crossinfect* OR cross-infection OR cross-infected OR cross-infecting OR "cross infection" OR "cross infected" OR "cross infecting" or hospitalised* or hospitalized* or hospitalisation* or hospitalization*))

Searches
5 abstract:((pneumonia OR pneumonias) AND ("healthcare acquire" OR "healthcare acquired" OR "healthcare acquiring" OR "healthcare onset" OR "healthcare associate" OR "healthcare associated" OR "healthcare associating"))
6 abstract:((pneumonia OR pneumonias) AND ("health care acquire" OR "health care acquired" OR "health care acquiring" OR "health care onset" OR "health care associate" OR "health care associated" OR "health care associating"))
7 abstract:((pneumonia OR pneumonias) AND ("hospital acquire" OR "hospital acquired" OR "hospital acquiring" OR "hospital onset" OR "hospital associate" OR "hospital associated" OR "hospital associating"))
8 abstract:((pneumonia OR pneumonias) AND ("inpatient acquire" OR "inpatient acquired" OR "inpatient acquiring" OR "inpatient onset" OR "inpatient associate" OR "inpatient associated" OR "inpatient associating"))
9 abstract:((pneumonia OR pneumonias) AND (healthcare-acquire OR healthcare-acquired OR healthcare-acquiring OR healthcare-onset OR healthcare-associate OR healthcare-associated OR healthcare-associating))
10 abstract:((pneumonia OR pneumonias) AND (health-care-acquire OR health-care-acquired OR health-care-acquiring OR health-care-onset OR health-care-associate OR health-care-associated OR health-care-associating))
11 abstract:((pneumonia OR pneumonias) AND (hospital-acquire OR hospital-acquired OR hospital-acquiring OR hospital-onset OR hospital-associate OR hospital-associated OR hospital-associating))
12 abstract:((pneumonia OR pneumonias) AND (inpatient-acquire OR inpatient-acquired OR inpatient-acquiring OR inpatient-onset OR inpatient-associate OR inpatient-associated OR inpatient-associating))
13 abstract:((pneumonia OR pneumonias) AND (CAP OR community* OR communities* OR outpatient* OR nonhospital* OR "non hospital" OR non-hospital OR "non hospitalised" OR non-hospitalised OR "non hospitalized" OR non-hospitalized OR "non hospitalisation" OR non-hospitalisation OR "non hospitalization" OR non-hospitalization))
14 abstract:((pneumonia OR pneumonias) AND (bacterial* OR chlamydial* OR mycoplasma* OR pneumococcal* OR rickettsial* OR staphylococcal* OR staphylococcus* OR necrotiz* OR necrotis* OR viral* OR organizing* OR organising* OR cryptogenic* OR bilateral* OR granulomatous* OR infectious* OR interstitial* OR neonatal* OR obstructive* OR lobar* OR escherichia* OR haemophilus* OR hemophilus* OR influenzae* OR nocardiosis* OR streptococcus* OR streptococcal*))
This is the final search as formatted by Epistemonikos:
title:((bronchopneumonia* OR pleuropneumonia* OR broncho-pneumonia OR pleuro-pneumonia OR broncho-pneumonias OR pleuro-pneumonias OR "broncho pneumonia" OR "pleuro pneumonia" OR "broncho pneumonias" OR "pleuro pneumonias")) OR abstract:((bronchopneumonia* OR pleuropneumonia* OR broncho-pneumonia OR pleuro-pneumonia OR broncho-pneumonias OR pleuro-pneumonias OR "broncho pneumonia" OR "pleuro pneumonia" OR "broncho pneumonias" OR "pleuro pneumonias")) OR title:((pneumonia OR pneumonias)) OR abstract:(((pneumonia OR pneumonias) AND (HAP OR nosocomial* OR crossinfect* OR cross-infection OR cross-infected OR cross-infecting OR "cross infection" OR "cross infected" OR "cross infecting" OR hospitalised* OR hospitalized* OR hospitalisation* OR hospitalization*))) OR abstract:(((pneumonia OR pneumonias) AND ("healthcare acquire" OR "healthcare acquired" OR "healthcare acquiring" OR "healthcare onset" OR "healthcare associate" OR "healthcare associated" OR "healthcare associating"))) OR abstract:(((pneumonia OR pneumonias) AND ("health care acquire" OR "health care acquired" OR "health care acquiring" OR "health care onset" OR "health care associate" OR "health care associated" OR "health care associating"))) OR abstract:(((pneumonia OR pneumonias) AND ("hospital acquire" OR "hospital acquired" OR "hospital acquiring" OR "hospital onset" OR "hospital associate" OR "hospital associated"

Searches
OR "hospital associating"))) OR abstract:(((pneumonia OR pneumonias) AND ("inpatient acquire" OR "inpatient acquired" OR "inpatient acquiring" OR "inpatient onset" OR "inpatient associate" OR "inpatient associated" OR "inpatient associating"))) OR abstract:(((pneumonia OR pneumonias) AND (healthcare-acquire OR healthcare-acquired OR healthcare-acquiring OR healthcare-onset OR healthcare-associate OR healthcare-associated OR healthcare-associating))) OR abstract:(((pneumonia OR pneumonias) AND (health-care-acquire OR health-care-acquired OR health-care-acquiring OR health-care-onset OR health-care-associate OR health-care-associated OR health-care-associating))) OR abstract:(((pneumonia OR pneumonias) AND (hospital-acquire OR hospital-acquired OR hospital-acquiring OR hospital-onset OR hospital-associate OR hospital-associated OR hospital-associating))) OR abstract:(((pneumonia OR pneumonias) AND (inpatient-acquire OR inpatient-acquired OR inpatient-acquiring OR inpatient-onset OR inpatient-associate OR inpatient-associated OR inpatient-associating))) OR abstract:(((pneumonia OR pneumonias) AND (CAP OR community* OR communities* OR outpatient* OR nonhospital* OR "non hospital" OR non-hospital OR "non hospitalised" OR non-hospitalised OR "non hospitalized" OR non-hospitalized OR "non hospitalisation" OR non-hospitalisation OR "non hospitalization" OR non-hospitalization))) OR abstract:(((pneumonia OR pneumonias) AND (bacterial* OR chlamydial* OR mycoplasma* OR pneumococcal* OR rickettsial* OR staphylococcal* OR staphylococcus* OR necrotiz* OR necrotis* OR viral* OR organizing* OR organising* OR cryptogenic* OR bilateral* OR granulomatous* OR infectious* OR interstitial* OR neonatal* OR obstructive* OR lobar* OR escherichia* OR haemophilus* OR hemophilus* OR influenzae* OR nocardiosis* OR streptococcus* OR streptococcal*))) **Results:** Total: 48055 Apply Publication Year limits of 2014-2024: 30820 Download 1: Apply Publication type - Systematic Review: 2307 Download 2: Apply Publication type - Broad Synthesis: 223 Download 3: Apply Publication type - Structured Summary: 41 **Note:** The re-run search covered the whole timespan 2014-2024 as the phrases in the free text were updated to use a version with a hyphen and to spell out the words rather than truncating them. The main search had used Publication Year limits of 2014-2023.

Part 2A: Effectiveness and prognostic evidence searches (adults)

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	23/02/2024	Wiley	Cochrane Central Register of Controlled Trials Issue 2 of 12, February 2024	337
Embase	23/02/2024	Ovid	Embase 1974 to 2024 February 22	2838

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
MEDLINE ALL	23/02/2024	Ovid	Ovid MEDLINE(R) ALL 1946 to February 22, 2024	2043

Additional search techniques

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Forward citation searching	22/02/2024	Web of Science (WOS) Core Collection (1990-present)	Data updated 2024-02-19	216
Reference list checking	22/02/2024	Web of Science (WOS) Core Collection (1990-present)	Data updated 2024-02-19	34
Reference list checking post search	14/03/2024, 20/03/2024 and 22/04/2024	N/A	N/A	10

Search strategy history

Database name: Cochrane Central Register of Controlled Trials (CENTRAL)

Searches	
#1	[mh ^pneumonia] or [mh ^bronchopneumonia] or [mh ^pleuropneumonia] or [mh ^"pneumonia, bacterial"] or [mh ^"chlamydial pneumonia"] or [mh ^"pneumonia, mycoplasma"] or [mh ^"pneumonia, pneumococcal"] or [mh ^"pneumonia, staphylococcal"] or [mh ^"pneumonia, necrotizing"] or [mh ^"pneumonia, viral"] or [mh ^"organizing pneumonia"] or [mh ^"healthcare-associated pneumonia"] 4393
#2	(pneumonia or pneumonias or bronchopneumon* or pleuropneumon*):ti,ab 15537
#3	#1 or #2 16778
#4	[mh ^"c-reactive protein"] 6340
#5	(((c NEXT react*) or creact*) NEAR/2 protein*):ti,ab 20618
#6	CRP:ti,ab 22849
#7	[mh ^Procalcitonin] 109
#8	[mh ^Calcitonin] 801
#9	(Procalcitonin* or (Pro NEXT calcitonin*) or ProCT or "Pro CT" or calcitonin1 or "calcitonin 1"):ti,ab 1459
#10	(Calcitonin* NEAR/3 (precursor* or "polypeptide alpha")):ti,ab 5
#11	([mh ^"Lymphocyte Count"] or [mh ^Lymphocytes]) and [mh ^Neutrophils] 246

Searches
#12 (Neutrophil* NEAR/3 lymphocyte* NEAR/2 (ratio or ratios or threshold or count* or relation* or relative*)):ti,ab 985
#13 NLR:ti,ab 581
#14 {or #4-#13} 35026
#15 #3 and #14 1227
#16 [mh ^"Respiratory Care Units"] or [mh ^"Respiratory Therapy Department, Hospital"] or [mh "Respiratory therapy"] 12017
#17 [mh ^hospitalization] or [mh ^hospitals] or [mh ^"secondary care"]9227
#18 [mh ^"Emergency Service, Hospital"] or [mh ^"Emergency Treatment"] or [mh ^"Emergency Medical Services"] or [mh "Emergency Medicine"] or [mh ^"Intensive Care Units"] 9462
#19 [mh ^"critical pathways"] or [mh ^"Critical Care"] 2946
#20 [mh ^"Referral and Consultation"] or [mh ^Triage] or [mh ^"patient transfer"] or [mh ^"Gatekeeping"]3448
#21 [mh ^"Clinical Decision-Making"] or [mh ^"Practice Patterns, Physicians'"] 2649
#22 [mh ^"Patient acuity"] or [mh ^"Patient Discharge"] or [mh ^"Patient Readmission"] or [mh ^Retreatment] 5241
#23 [mh ^"Treatment Failure"] or [mh ^"Treatment Outcome"] 193409
#24 [mh mortality] 18841
#25 [mh ^"Drug Administration Schedule"] or [mh ^"Duration of Therapy"] or [mh ^"Episode of Care"] or [mh ^"Length of Stay"] 37825
#26 [mh ^"Inappropriate prescribing"] 279
#27 [mh ^"anti-infective agents"] or [mh "exp anti-bacterial agents"] or [mh "anti-infective agents, local"] 5947
#28 (hospitaliz* or hospitalis* or rehospitalis* or rehospitaliz*):ti,ab 60610
#29 ((patient* or inpatient*) NEAR/3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or rebound* or revisit* or declin* or worsen* or remission* or deteriorat* or escalat* or deescalat* or acuity* or triage* or triaging* or morbidit*)):ti,ab 54351
#30 ((hospital* or ICU or (intensive NEXT care*) or (intensive NEXT treatment*) or ITU or (high NEXT dependency*) or HDU or (critical NEXT care*) or "A&E" or (secondary NEXT care*) or (respiratory NEXT care*) or (accident near/1 emergenc*)) NEAR/3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or revisit* or escalat* or deescalat* or triage* or triaging* or duration* or length* or episod* or period*)):ti,ab 62093
#31 ((specialist* or specialized* or specialised* or emergenc* or secondary*) NEAR/2 (care* or service* or facility* or facilities* or ward or wards or unit or units or department* or clinic or clinics) NEAR/3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or revisit* or escalat* or deescalat* or triage* or triaging* or duration* or length* or episod* or period*)):ti,ab 2901
#32 ((invasive* or artificial*) NEAR/3 (respirat* or ventilat*)):ti,ab 4882
#33 ((discharg* or referral* or referred*) NEAR/3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or extend* or prolong* or interval* or schedul*)):ti,ab 9091
#34 (hospital* NEAR/3 ((stay* or episod*) NEAR/3 (time* or timing* or duration* or length* or short* or medium* or long* or prolong* or extend*))):ti,ab 22121
#35 ("length of stay" or "episode of care"):ti,ab 13838

Searches
#36 ((therap* or intervention* or treatment*) NEAR/3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or duration* or length* or short* or medium* or long* or episod* or extend* or prolong* or interval* or gradual* or persist* or escalat* or deescalat* or (step* NEXT up) or (step* NEXT down) or stepup or stepdown or fail* or outcome* or admin* or schedul* or initiat* or start* or strateg* or unnecessar* or standby or "stand by")):ti,ab 284807
#37 (((anti NEXT infectiv*) or antiinfectiv* or antibacter* or (anti NEXT bacter*) or antimicrobial* or (anti NEXT microbial*) or antibiot* or (anti NEXT biot*)) NEAR/3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or duration* or length* or short* or medium* or long* or episod* or extend* or prolong* or interval* or gradual* or persist* or escalat* or deescalat* or (step* NEXT up) or (step* NEXT down) or stepup or stepdown or fail* or outcome* or admin* or schedul* or initiat* or start* or strateg* or unnecessar* or standby or "stand by" or rescue* or misuse* or overuse* or (over NEXT use*) or overprescri* or (over NEXT prescri*) or deprescri* or abus* or steward* or resist*)):ti,ab 11093
#38 ((care* or treatment* or critical*) NEAR/2 (pathway* or path or paths)):ti,ab 1852
#39 ((mortality* or death*) NEAR/3 (predict* or risk* or prognos*)):ti,ab 14625
#40 ((severity* or severe* or nonsevere*) NEAR/3 (predict* or assess* or stratif* or risk*)):ti,ab 11195
#41 {or #16-#40} 601486
#42 #15 and #41 928
#43 ((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an494409
#44 #42 not #43 523
#45 "conference":pt 236547
#46 #44 not #45 421
#47 #44 not #45 in Trials 419
Post search filter: Date added to CENTRAL trials database: 01/03/2014 to 01/02/2024 337
Note: a version with Line 27 corrected was run and the additional 6 papers identified. These were checked in EPPI-R and they were all already available in the results so they were not downloaded again. The corrected line was used in the re-runs:
[mh ^"anti-infective agents"] or [mh "anti-bacterial agents"] or [mh "anti-infective agents, local"]

Database name: Embase

Searches
1 pneumonia/ or bilateral pneumonia/ or bronchopneumonia/ or granulomatous pneumonia/ or infectious pneumonia/ or interstitial pneumonia/ or necrotizing pneumonia/ or neonatal pneumonia/ or obstructive pneumonia/ or organizing pneumonia/ or bacterial pneumonia/ or community acquired pneumonia/ or health care associated pneumonia/ or exp lobar pneumonia/ or virus pneumonia/ or chlamydial pneumonia/ or escherichia coli pneumonia/ or haemophilus influenzae pneumonia/ or pulmonary nocardiosis/ or

Searches
mycoplasma pneumonia/ or exp staphylococcal pneumonia/ or exp streptococcus pneumonia/ or hospital acquired pneumonia/ 319791
2 (pneumonia or pneumonias or bronchopneumon* or pleuropneumon*).ti,ab. 237264
3 1 or 2 403008
4 *C reactive protein/ 28799
5 (("c react*" or creact*) adj2 protein*).ti,ab. 137354
6 CRP.ti,ab. 133451
7 *Procalcitonin/ 6248
8 (Procalcitonin* or "Pro calcitonin*" or ProCT or "Pro CT" or calcitonin1 or "calcitonin 1").ti,ab. 16076
9 (Calcitonin* adj3 (precursor* or "polypeptide alpha")).ti,ab. 235
10 *neutrophil lymphocyte ratio/ 8143
11 (Neutrophil* adj3 lymphocyte* adj2 (ratio or ratios or threshold or count* or relation* or relative*)).ti,ab. 22429
12 NLR.ti,ab. 22045
13 or/4-12 233220
14 3 and 13 12036
15 respiratory care/ or respiratory care practice/ or exp artificial ventilation/ 260204
16 hospitalization/ or hospital care/ or hospital patient/ or secondary health care/ 777968
17 emergency ward/ or high dependency unit/ or emergency health service/ or hospital emergency service/ or emergency treatment/ or emergency care/ or evidence based emergency medicine/ or emergency medicine/ 427115
18 intensive care/ or intensive care unit/ or medical intensive care unit/ 365627
19 clinical pathway/ or critical care outcome/ 10750
20 patient referral/ or patient triage/ 168362
21 clinical decision making/ or clinical practice/ 439663
22 patient acuity/ or hospital discharge/ or hospital admission/ or hospital readmission/ or retreatment/ 538480
23 treatment failure/ or treatment outcome/ or clinical outcome/ 1463216
24 exp mortality/ 1414760
25 drug administration/ or acute drug administration/ or treatment duration/ or "length of stay"/636392
26 unnecessary prescribing/ or overprescribing/ 525
27 antiinfective agent/ or exp antibiotic agent/ or exp topical antiinfective agent/ 2653965
28 (hospitaliz* or hospitalis* or rehospitalis* or rehospitaliz*).ti,ab. 585021
29 ((patient* or inpatient*) adj3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or rebound* or revisit* or declin* or worsen* or remission* or deteriorat* or escalat* or deescalat* or acuity* or triage* or triaging* or morbidit*)).ti,ab. 750434
30 ((hospital* or ICU or "intensive care*" or "intensive treatment*" or ITU or "high dependency*" or HDU or "critical care*" or "A&E" or "secondary care*" or "respiratory care*" or "accident and emergenc*") adj3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or

Searches
discharg* or retreat* or readmission* or readmit* or revisit* or escalat* or deescalat* or triage* or triaging* or duration* or length* or episod*)).ti,ab. 598884
31 ((specialist* or specialized* or specialised* or emergenc* or secondary*) adj2 (care* or service* or facility* or facilities* or ward or wards or unit or units or department* or clinic or clinics) adj3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or revisit* or escalat* or deescalat* or triage* or triaging* or duration* or length* or episod*)).ti,ab. 39922
32 ((invasive* or artificial*) adj3 (respirat* or ventilat*)).ti,ab. 35066
33 ((discharg* or referral* or referred*) adj3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or extend* or prolong* or interval* or schedul* or period*)).ti,ab. 68760
34 (hospital* adj3 ((stay* or episod*) adj3 (time* or timing* or duration* or length* or short* or medium* or long* or prolong* or extend* or period*))).ti,ab. 151801
35 ("length of stay" or "episode of care").ti,ab. 156279
36 ((therap* or intervention* or treatment*) adj3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or duration* or length* or short* or medium* or long* or episod* or extend* or prolong* or interval* or gradual* or persist* or escalat* or deescalat* or "step* up" or "step* down" or stepup or stepdown or fail* or outcome* or admin* or schedul* or initiat* or start* or strateg* or unnecessar* or standby or "stand by")).ti,ab. 2111831
37 (("anti infectiv*" or antiinfectiv* or antibacter* or "anti bacter*" or antimicrobial* or "anti microbial*" or antibiot* or "anti biot*") adj3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or duration* or length* or short* or medium* or long* or episod* or extend* or prolong* or interval* or gradual* or persist* or escalat* or deescalat* or "step* up" or "step* down" or stepup or stepdown or fail* or outcome* or admin* or schedul* or initiat* or start* or strateg* or unnecessar* or standby or "stand by" or rescue* or misuse* or overuse* or "over use*" or overprescri* or "over prescri*" or deprescri* or abus* or steward* or resist*)).ti,ab. 243497
38 ((care* or treatment* or critical*) adj2 (pathway* or path or paths)).ti,ab. 40998
39 ((mortality* or death*) adj3 (predict* or risk* or prognos*)).ti,ab. 280800
40 ((severity* or severe* or nonsevere*) adj3 (predict* or assess* or stratif* or risk*)).ti,ab. 131734
41 or/15-40 8986675
42 14 and 41 9772
43 limit 42 to english language 9064
44 (letter or editorial).pt. 2104366
45 43 not 44 8940
46 Case report/ 2969074
47 45 not 46 7398
48 nonhuman/ not human/ 5386407
49 47 not 48 7313
50 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5844635
51 49 not 50 4917
52 random:.tw. 2034866
53 placebo:.mp. 533693
54 double-blind:.tw. 249531
55 or/52-54 2316370

Searches		
56	51 and 55	595
57	predict.ti.	101949
58	(validat* or rule*).ti,ab.	1362007
59	(predict* and (outcome* or risk* or model*)).ti,ab.	1707981
60	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.	5968590
61	decision*.ti,ab. and Statistical model/	8131
62	(decision* and (model* or clinical*)).ti,ab.	376414
63	(prognostic* and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.	486432
64	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.	1532114
65	Receiver operating characteristic/	222711
66	prognosis/ or prognostic assessment/	703006
67	or/57-66	8596281
68	51 and 67	3132
69	56 or 68	3452
70	limit 69 to dc=20140301-20240229	2838

Database name: MEDLINE ALL

Searches		
1	pneumonia/ or bronchopneumonia/ or pleuropneumonia/ or pneumonia, bacterial/ or chlamydial pneumonia/ or pneumonia, mycoplasma/ or pneumonia, pneumococcal/ or pneumonia, staphylococcal/ or pneumonia, necrotizing/ or pneumonia, viral/ or organizing pneumonia/ or healthcare-associated pneumonia/	124812
2	(pneumonia or pneumonias or bronchopneumon* or pleuropneumon*).ti,ab.	161695
3	1 or 2	231640
4	c-reactive protein/	55385
5	(("c react*" or creact*) adj2 protein*).ti,ab.	93379
6	CRP.ti,ab.	66687
7	Procalcitonin/	1995
8	Calcitonin/	16297
9	(Procalcitonin* or "Pro calcitonin*" or ProCT or "Pro CT" or calcitonin1 or "calcitonin 1").ti,ab.	9697
10	(Calcitonin* adj3 (precursor* or "polypeptide alpha")).ti,ab.	170
11	(Lymphocyte Count/ or Lymphocytes/) and Neutrophils/	10652
12	(Neutrophil* adj3 lymphocyte* adj2 (ratio or ratios or threshold or count* or relation* or relative*)).ti,ab.	14558
13	NLR.ti,ab.	14682
14	or/4-13	162232
15	3 and 14	6160
16	Respiratory Care Units/ or Respiratory Therapy Department, Hospital/ or exp Respiratory therapy/	136128
17	hospitalization/ or hospitals/ or secondary care/	239329

Searches
18 Emergency Service, Hospital/ or Emergency Treatment/ or Emergency Medical Services/ or exp Emergency Medicine/ or Intensive Care Units/ 224519
19 critical pathways/ or Critical Care/ 69428
20 "Referral and Consultation"/ or Triage/ or patient transfer/ or Gatekeeping/ 100863
21 Clinical Decision-Making/ or Practice Patterns, Physicians'/ 81533
22 Patient acuity/ or Patient Discharge/ or Patient Readmission/ or Retreatment/ 72647
23 Treatment Failure/ or Treatment Outcome/ 1208331
24 exp mortality/ 426038
25 Drug Administration Schedule/ or Duration of Therapy/ or Episode of Care/ or Length of Stay/ 209005
26 Inappropriate prescribing/ 4733
27 anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/ 1110784
28 (hospitaliz* or hospitalis* or rehospitalis* or rehospitaliz*).ti,ab. 357069
29 ((patient* or inpatient*) adj3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or rebound* or revisit* or declin* or worsen* or remission* or deteriorat* or escalat* or deescalat* or acuity* or triage* or triaging* or morbidit*)).ti,ab. 406221
30 ((hospital* or ICU or "intensive care*" or "intensive treatment*" or ITU or "high dependency*" or HDU or "critical care*" or "A&E" or "secondary care*" or "respiratory care*" or "accident and emergenc*") adj3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or revisit* or escalat* or deescalat* or triage* or triaging* or duration* or length* or episod*)).ti,ab. 362534
31 ((specialist* or specialized* or specialised* or emergenc* or secondary*) adj2 (care* or service* or facility* or facilities* or ward or wards or unit or units or department* or clinic or clinics) adj3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or revisit* or escalat* or deescalat* or triage* or triaging* or duration* or length* or episod*)).ti,ab. 24230
32 ((invasive* or artificial*) adj3 (respirat* or ventilat*)).ti,ab. 21732
33 ((discharg* or referral* or referred*) adj3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or extend* or prolong* or interval* or schedul* or period*)).ti,ab. 39548
34 (hospital* adj3 ((stay* or episod*) adj3 (time* or timing* or duration* or length* or short* or medium* or long* or prolong* or extend* or period*))).ti,ab. 93047
35 ("length of stay" or "episode of care").ti,ab. 83140
36 ((therap* or intervention* or treatment*) adj3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or duration* or length* or short* or medium* or long* or episod* or extend* or prolong* or interval* or gradual* or persist* or escalat* or deescalat* or "step* up" or "step* down" or stepup or stepdown or fail* or outcome* or admin* or schedul* or initiat* or start* or strateg* or unnecessar* or standby or "stand by")).ti,ab. 1393828
37 (("anti infectiv*" or antiinfectiv* or antibacter* or "anti bacter*" or antimicrobial* or "anti microbial*" or antibiot* or "anti biot*") adj3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or duration* or length* or short* or medium* or long* or episod* or extend* or prolong* or interval* or gradual* or persist* or escalat* or deescalat* or "step* up" or "step* down" or stepup or stepdown or fail*

Searches
or outcome* or admin* or schedul* or initiat* or start* or strateg* or unnecessar* or standby or "stand by" or rescue* or misuse* or overuse* or "over use*" or overprescri* or "over prescri*" or deprescri* or abus* or steward* or resist*)).ti,ab. 186806
38 ((care* or treatment* or critical*) adj2 (pathway* or path or paths)).ti,ab. 26381
39 ((mortality* or death*) adj3 (predict* or risk* or prognos*)).ti,ab. 180341
40 ((severity* or severe* or nonsevere*) adj3 (predict* or assess* or stratif* or risk*)).ti,ab. 84360
41 or/16-40 5172211
42 15 and 41 4346
43 limit 42 to english language 3893
44 limit 43 to (letter or historical article or comment or editorial or news or case reports) 327
45 43 not 44 3566
46 Animals/ not (Animals/ and Humans/) 5164074
47 45 not 46 3542
48 exp Randomized Controlled Trial/ 610842
49 randomi?ed.mp. 1106080
50 placebo.mp. 254014
51 or/48-50 1173312
52 47 and 51 326
53 predict.ti. 67313
54 (validat* or rule*).ti,ab. 972536
55 (predict* and (outcome* or risk* or model*)).ti,ab. 1214216
56 ((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab. 4314415
57 decision*.ti,ab. and Logistic models/ 5944
58 (decision* and (model* or clinical*)).ti,ab. 259724
59 (prognostic* and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab. 314133
60 (stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab. 1136678
61 ROC curve/ 72132
62 Prognosis/ 606201
63 or/53-62 6396970
64 47 and 63 2271
65 52 or 64 2443
66 limit 65 to ed=20140301-20240229 1633
67 limit 65 to dt=20140301-20240229 1993
68 66 or 67 2043

Additional search techniques

Forward citation searching

Date of search	22/02/24
How the seed papers were identified	Identified from the papers selected for this question from the search for systematic

	reviews; the scoping searches for this guideline; and the included papers in CG191.
Databases used	Web of Science (WOS) Core Collection (1990-present) • Science Citation Index Expanded (1990-present) • Social Sciences Citation Index (1990-present) • Arts & Humanities Citation Index (1990-present) • Emerging Sources Citation Index (2019-present)
Date of last update	Data updated 2024-02-19
How results were managed	Only those references that could be accessed through the NICE subscription to WOS were added to the search results. Duplicates were removed from the marked list in WOS before downloading the results.
How the results were selected	Included any papers potentially relevant to ProCT, CRP and NLR in pneumonia, in adults only. Did not make any decisions based on the location of the study. Did not include any papers about COVID-19, tuberculosis, sepsis or other conditions but did include general LRTI papers. Did not include any papers that were about methods or epidemiology. Did not include animal studies, letters or editorials. Did not include anything that was not written in English.
List of seed papers used	Albrich WC et al. (2012) Effectiveness and safety of procalcitonin-guided antibiotic therapy in lower respiratory tract infections in "real life": an international, multicenter poststudy survey (proreal). Archives of Internal Medicine, 172(9), 715-22. Alzoubi O et al. (2021) Association between neutrophil to lymphocyte ratio and mortality among community acquired pneumonia patients: a meta-analysis. Monaldi Archives for Chest Disease, 92(3). Boussekey N, et al. (2006) Procalcitonin kinetics in the prognosis of severe community-acquired pneumonia. Intensive Care Medicine, 32(3):469-472.

	Bruns AHW et al. (2008) Usefulness of consecutive C-reactive protein measurements in follow-up of severe community-acquired pneumonia. European Respiratory Journal, 32(3):726-732. Colak A et al. (2017) Procalcitonin and crp as biomarkers in discrimination of community-acquired pneumonia and exacerbation of copd. Journal of Medical Biochemistry, 36, 122-126. Chalmers JD et al. (2008) C-reactive protein is an independent predictor of severity in community-acquired pneumonia. American Journal of Medicine, 121(3), 219-225. Christ-Crain M (2004) Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet, 363(9409), 600-7. Christ-Crain M et al. (2006) Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. American Journal of Respiratory and Critical Care Medicine, 174(1), 84-93. Coelho LM et al. (2012) Patterns of c-reactive protein RATIO response in severe community-acquired pneumonia: a cohort study. Critical Care, 16(2), R53. Kamat IS et al. (2020) Procalcitonin to distinguish viral from bacterial pneumonia: a systematic review and meta-analysis. Clinical Infectious Diseases, 70(3), 538-542. Kuikel S et al. (2022) Neutrophil-lymphocyte ratio as a predictor of adverse outcome in patients with community-acquired pneumonia: a systematic review. Health Science Reports, 5(3), e630. Liu D et al. (2016) Prognostic value of procalcitonin in pneumonia: a systematic review and meta-analysis. Respirology, 21(2), 280-8. Menendez R et al. (2008) Markers of treatment failure in hospitalised community

	acquired pneumonia. Thorax, 63(5), 447-452. Menendez R et al. (2009) Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia. Thorax, 64(7), 587-591. Pfister R et al. (2014) Procalcitonin for diagnosis of bacterial pneumonia in critically ill patients during 2009 h1n1 influenza pandemic: a prospective cohort study, systematic review and individual patient data meta-analysis. Critical Care, 18(2), R44. Scalera NM & File TM (2013) Determining the duration of therapy for patients with community-acquired pneumonia. Current Infectious Disease Reports, 15(2), 191-5. Schuetz P et al. (2009) Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the prohosp randomized controlled trial. JAMA, 302(10), 1059-66. Shojaan H et al. (2023) Diagnostic value of the neutrophil lymphocyte ratio in discrimination between tuberculosis and bacterial community acquired pneumonia: a meta-analysis. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases, 33, 100395. Viasus D et al. (2016) Biomarkers for predicting short-term mortality in community-acquired pneumonia: a systematic review and meta-analysis. Journal of Infection, 72(3), 273-82. Wu MH et al. (2013) Can procalcitonin tests aid in identifying bacterial infections associated with influenza pneumonia? a systematic review and meta-analysis. Influenza & Other Respiratory Viruses, 7(3), 349-55.
No. of results	216

Reference list checking

Date of search	22/02/24

How the seed papers were identified	Identified from the papers selected for this question from the search for systematic reviews; the scoping searches for this guideline; and the included papers in CG191.
Databases used	Web of Science (WOS) Core Collection (1990-present) • Science Citation Index Expanded (1990-present) • Social Sciences Citation Index (1990-present) • Arts & Humanities Citation Index (1990-present) • Emerging Sources Citation Index (2019-present)
Date of last update	Data updated 2024-02-19
How results were managed	Only those references that could be accessed through the NICE subscription to WOS were added to the search results. Duplicates were removed from the marked list in WOS before downloading the results.
How the results were selected	Included any papers potentially relevant to ProCT, CRP and NLR in pneumonia, in adults only. Did not make any decisions based on the location of the study. Did not include any papers about COVID-19, tuberculosis, sepsis or other conditions but did include general LRTI papers. Did not include any papers that were about methods or epidemiology. Did not include animal studies, letters or editorials. Did not include anything that was not written in English.
List of seed papers used	Alzoubi O et al. (2021) Association between neutrophil to lymphocyte ratio and mortality among community acquired pneumonia patients: a meta-analysis. Monaldi Archives for Chest Disease, 92(3). Colak A et al. (2017) Procalcitonin and crp as biomarkers in discrimination of community-acquired pneumonia and exacerbation of copd. Journal of Medical Biochemistry, 36, 122-126. Kamat IS et al. (2020) Procalcitonin to distinguish viral from bacterial pneumonia: a systematic review and meta-analysis. Clinical Infectious Diseases, 70(3), 538-542.

	Kuikel S et al. (2022) Neutrophil-lymphocyte ratio as a predictor of adverse outcome in patients with community-acquired pneumonia: a systematic review. Health Science Reports, 5(3), e630. Liu D et al. (2016) Prognostic value of procalcitonin in pneumonia: a systematic review and meta-analysis. Respirology, 21(2), 280-8. Pfister R et al. (2014) Procalcitonin for diagnosis of bacterial pneumonia in critically ill patients during 2009 h1n1 influenza pandemic: a prospective cohort study, systematic review and individual patient data meta-analysis. Critical Care, 18(2), R44. Shojaan H et al. (2023) Diagnostic value of the neutrophil lymphocyte ratio in discrimination between tuberculosis and bacterial community acquired pneumonia: a meta-analysis. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases, 33, 100395. Viasus D et al. (2016) Biomarkers for predicting short-term mortality in community-acquired pneumonia: a systematic review and meta-analysis. Journal of Infection, 72(3), 273-82.
No. of results	34

Reference list checking post search

Date of search	14/03/24, 20/03/24 and 22/04/24
How the seed papers were identified	In line with section 6.1 of the NICE manual (Ensuring relevant records are not missed) a further round of reference checking was undertaken after the main search. This used systematic reviews identified while screening the results for Part 2A (i.e. they were not taken directly from the SR search done in Part 1).
How results were managed	Studies included in the reviews were identified as potentially relevant from the results section and the accompanying charts. These were sourced using the bibliography. The studies were then added manually to EPPI-Reviewer using PubMed records.
No. of results	10

Part 2B: Effectiveness and prognostic evidence searches (children)

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	23/02/24	Wiley	Cochrane Central Register of Controlled Trials Issue 2 of 12, February 2024	69
Embase	23/02/24	Ovid	Embase 1974 to 2024 February 22	705
MEDLINE ALL	23/02/24	Ovid	Ovid MEDLINE(R) ALL 1946 to February 22, 2024	513

Additional search techniques

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Forward citation searching	22/02/24	Web of Science (WOS) Core Collection (1990-present)	Data updated 2024-02-19	89
Reference list checking	22/02/24	Web of Science (WOS) Core Collection (1990-present)	Data updated 2024-02-19	90

Search strategy history

Database name: Cochrane Central Register of Controlled Trials (CENTRAL)

Searches	
#1	[mh ^pneumonia] or [mh ^bronchopneumonia] or [mh ^pleuropneumonia] or [mh ^"pneumonia, bacterial"] or [mh ^"chlamydial pneumonia"] or [mh ^"pneumonia, mycoplasma"] or [mh ^"pneumonia, pneumococcal"] or [mh ^"pneumonia, staphylococcal"] or [mh ^"pneumonia, necrotizing"] or [mh ^"pneumonia, viral"] or [mh ^"organizing pneumonia"] or [mh ^"healthcare-associated pneumonia"] 4399
#2	(pneumonia or pneumonias or bronchopneumon* or pleuropneumon*):ti,ab 15670
#3	#1 or #2 16911
#4	[mh ^"c-reactive protein"] 6356
#5	(((c NEXT react*) or creact*) NEAR/2 protein*):ti,ab 20820

Searches
#6 CRP:ti,ab 23071
#7 [mh ^Procalcitonin] 110
#8 [mh ^Calcitonin] 801
#9 (Procalcitonin* or (Pro NEXT calcitonin*) or ProCT or "Pro CT" or calcitonin1 or "calcitonin 1"):ti,ab 1483
#10 (Calcitonin* NEAR/3 (precursor* or "polypeptide alpha")):ti,ab 6
#11 ([mh ^"Lymphocyte Count"] or [mh ^Lymphocytes]) and [mh ^Neutrophils] 247
#12 (Neutrophil* NEAR/3 lymphocyte* NEAR/2 (ratio or ratios or threshold or count* or relation* or relative*)):ti,ab 1009
#13 NLR:ti,ab 598
#14 {or #4-#13} 35352
#15 #3 and #14 1240
#16 [mh ^"Respiratory Care Units"] or [mh ^"Respiratory Therapy Department, Hospital"] or [mh "Respiratory therapy"] 12054
#17 [mh ^hospitalization] or [mh ^hospitals] or [mh ^"secondary care"]9260
#18 [mh ^"Emergency Service, Hospital"] or [mh ^"Emergency Treatment"] or [mh ^"Emergency Medical Services"] or [mh "Emergency Medicine"] or [mh ^"Intensive Care Units"] 9512
#19 [mh ^"critical pathways"] or [mh ^"Critical Care"] 2960
#20 [mh ^"Referral and Consultation"] or [mh ^Triage] or [mh ^"patient transfer"] or [mh ^"Gatekeeping"]3454
#21 [mh ^"Clinical Decision-Making"] or [mh ^"Practice Patterns, Physicians'"] 2656
#22 [mh ^"Patient acuity"] or [mh ^"Patient Discharge"] or [mh ^"Patient Readmission"] or [mh ^Retreatment] 5259
#23 [mh ^"Treatment Failure"] or [mh ^"Treatment Outcome"] 193930
#24 [mh mortality] 18860
#25 [mh ^"Drug Administration Schedule"] or [mh ^"Duration of Therapy"] or [mh ^"Episode of Care"] or [mh ^"Length of Stay"] 37835
#26 [mh ^"Inappropriate prescribing"] 279
#27 [mh ^"anti-infective agents"] or [mh "anti-bacterial agents"] or [mh "anti-infective agents, local"] 21857
#28 (hospitaliz* or hospitalis* or rehospitalis* or rehospitaliz*):ti,ab 61219
#29 ((patient* or inpatient*) NEAR/3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or rebound* or revisit* or declin* or worsen* or remission* or deteriorat* or escalat* or deescalat* or acuity* or triage* or triaging* or morbidit*)):ti,ab 54762
#30 ((hospital* or ICU or (intensive NEXT care*) or (intensive NEXT treatment*) or ITU or (high NEXT dependency*) or HDU or (critical NEXT care*) or "A&E" or (secondary NEXT care*) or (respiratory NEXT care*) or (accident near/1 emergenc*)) NEAR/3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or revisit* or escalat* or deescalat* or triage* or triaging* or duration* or length* or episod* or period*)):ti,ab 62654
#31 ((specialist* or specialized* or specialised* or emergenc* or secondary*) NEAR/2 (care* or service* or facility* or facilities* or ward or wards or unit or units or department* or clinic or clinics) NEAR/3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or

Searches
retreat* or readmission* or readmit* or revisit* or escalat* or deescalat* or triage* or triaging* or duration* or length* or episod* or period*)):ti,ab 2923
#32 ((invasive* or artificial*) NEAR/3 (respirat* or ventilat*)):ti,ab 4940
#33 ((discharg* or referral* or referred*) NEAR/3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or extend* or prolong* or interval* or schedul*)):ti,ab 9164
#34 (hospital* NEAR/3 ((stay* or episod*) NEAR/3 (time* or timing* or duration* or length* or short* or medium* or long* or prolong* or extend*))):ti,ab 22323
#35 ("length of stay" or "episode of care"):ti,ab 13960
#36 ((therap* or intervention* or treatment*) NEAR/3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or duration* or length* or short* or medium* or long* or episod* or extend* or prolong* or interval* or gradual* or persist* or escalat* or deescalat* or (step* NEXT up) or (step* NEXT down) or stepup or stepdown or fail* or outcome* or admin* or schedul* or initiat* or start* or strateg* or unnecessar* or standby or "stand by")):ti,ab 287349
#37 (((anti NEXT infectiv*) or antiinfectiv* or antibacter* or (anti NEXT bacter*) or antimicrobial* or (anti NEXT microbial*) or antibiot* or (anti NEXT biot*)) NEAR/3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or duration* or length* or short* or medium* or long* or episod* or extend* or prolong* or interval* or gradual* or persist* or escalat* or deescalat* or (step* NEXT up) or (step* NEXT down) or stepup or stepdown or fail* or outcome* or admin* or schedul* or initiat* or start* or strateg* or unnecessar* or standby or "stand by" or rescue* or misuse* or overuse* or (over NEXT use*) or overprescri* or (over NEXT prescri*) or deprescri* or abus* or steward* or resist*)):ti,ab 11191
#38 ((care* or treatment* or critical*) NEAR/2 (pathway* or path or paths)):ti,ab 1875
#39 ((mortality* or death*) NEAR/3 (predict* or risk* or prognos*)):ti,ab 14742
#40 ((severity* or severe* or nonsevere*) NEAR/3 (predict* or assess* or stratif* or risk*)):ti,ab 11302
#41 {or #16-#40} 611375
#42 #15 and #41 947
#43 [mh "pediatrics"] or [mh ^Infant] or [mh ^"Infant Health"] or [mh ^"Infant Welfare"] or [mh ^"Infant Care"] or [mh Child] or [mh "Child Behavior"] or [mh ^"Child Health"] or [mh ^"Child Welfare"] or [mh ^"Child Care"] or [mh ^Minors] or [mh ^" Child, Hospitalized"] 94452
#44 (pediatric* or paediatric* or infan* or baby* or babies or toddler* or (pre NEXT school*) or preschool* or kindergar* or child* or minor or minors or boy* or girl* or kid or kids):ti,ab 236191
#45 [mh ^Adolescent] or [mh ^"Adolescent Behavior"] or [mh ^"Adolescent Health"] or [mh ^Puberty] or [mh ^"Adolescent, Hospitalized"] 136635
#46 ((under NEXT 18*) or (under NEXT eighteen*)):ti,ab 16890
#47 (adolescen* or pubescen* or prepubescen* or puberty* or prepubert* or teen* or preteen* or juvenil* or youth* or youngster* or schoolchild* or (school NEXT age*) or schoolage* or underage* or (under NEXT age*)):ti,ab 51523
#48 (young* NEAR/1 (adult* or person* or people* or men or man or women* or woman* or male* or female* or patient* or inpatient* or outpatient*)):ti,ab 29578
#49 {or #43-#48} 393206
#50 #42 and #49 232
#51 ((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS

Searches
or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an498244
#52 #50 not #51 112
#53 "conference":pt 239278
#54 #52 not #53 103
#55 #52 not #53 in Trials 102
#56 #52 not #53 with Publication Year from 2014 to 2024, in Trials 69

Database name: Embase

Searches
1 pneumonia/ or bilateral pneumonia/ or bronchopneumonia/ or granulomatous pneumonia/ or infectious pneumonia/ or interstitial pneumonia/ or necrotizing pneumonia/ or neonatal pneumonia/ or obstructive pneumonia/ or organizing pneumonia/ or bacterial pneumonia/ or community acquired pneumonia/ or health care associated pneumonia/ or exp lobar pneumonia/ or virus pneumonia/ or chlamydial pneumonia/ or escherichia coli pneumonia/ or haemophilus influenzae pneumonia/ or pulmonary nocardiosis/ or mycoplasma pneumonia/ or exp staphylococcal pneumonia/ or exp streptococcus pneumonia/ or hospital acquired pneumonia/ 319791
2 (pneumonia or pneumonias or bronchopneumon* or pleuropneumon*).ti,ab. 237264
3 1 or 2 403008
4 *C reactive protein/ 28799
5 (("c react*" or creact*) adj2 protein*).ti,ab. 137354
6 CRP.ti,ab. 133451
7 *Procalcitonin/ 6248
8 (Procalcitonin* or "Pro calcitonin*" or ProCT or "Pro CT" or calcitonin1 or "calcitonin 1").ti,ab. 16076
9 (Calcitonin* adj3 (precursor* or "polypeptide alpha")).ti,ab. 235
10 *neutrophil lymphocyte ratio/ 8143
11 (Neutrophil* adj3 lymphocyte* adj2 (ratio or ratios or threshold or count* or relation* or relative*)).ti,ab. 22429
12 NLR.ti,ab. 22045
13 or/4-12 233220
14 3 and 13 12036
15 respiratory care/ or respiratory care practice/ or exp artificial ventilation/ 260204
16 hospitalization/ or hospital care/ or hospital patient/ or secondary health care/ 777968
17 emergency ward/ or high dependency unit/ or emergency health service/ or hospital emergency service/ or emergency treatment/ or emergency care/ or evidence based emergency medicine/ or emergency medicine/ 427115
18 intensive care/ or intensive care unit/ or medical intensive care unit/ 365627
19 clinical pathway/ or critical care outcome/ 10750
20 patient referral/ or patient triage/ 168362
21 clinical decision making/ or clinical practice/ 439663
22 patient acuity/ or hospital discharge/ or hospital admission/ or hospital readmission/ or retreatment/ 538480

Searches
23 treatment failure/ or treatment outcome/ or clinical outcome/ 1463216
24 exp mortality/ 1414760
25 drug administration/ or acute drug administration/ or treatment duration/ or "length of stay"/636392
26 unnecessary prescribing/ or overprescribing/ 525
27 antiinfective agent/ or exp antibiotic agent/ or exp topical antiinfective agent/ 2653965
28 (hospitaliz* or hospitalis* or rehospitalis* or rehospitaliz*).ti,ab. 585021
29 ((patient* or inpatient*) adj3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or rebound* or revisit* or declin* or worsen* or remission* or deteriorat* or escalat* or deescalat* or acuity* or triage* or triaging* or morbidit*)).ti,ab. 750434
30 ((hospital* or ICU or "intensive care*" or "intensive treatment*" or ITU or "high dependency*" or HDU or "critical care*" or "A&E" or "secondary care*" or "respiratory care*" or "accident and emergenc*") adj3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or revisit* or escalat* or deescalat* or triage* or triaging* or duration* or length* or episod* or period*)).ti,ab. 619009
31 ((specialist* or specialized* or specialised* or emergenc* or secondary*) adj2 (care* or service* or facility* or facilities* or ward or wards or unit or units or department* or clinic or clinics) adj3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or escalat* or revisit* or deescalat* or triage* or triaging* or duration* or length* or episod* or period*)).ti,ab. 40566
32 ((invasive* or artificial*) adj3 (respirat* or ventilat*)).ti,ab. 35066
33 ((discharg* or referral* or referred*) adj3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or extend* or prolong* or interval* or schedul*)).ti,ab. 61727
34 (hospital* adj3 ((stay* or episod*) adj3 (time* or timing* or duration* or length* or short* or medium* or long* or prolong* or extend*))).ti,ab.151147
35 ("length of stay" or "episode of care").ti,ab. 156279
36 ((therap* or intervention* or treatment*) adj3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or duration* or length* or short* or medium* or long* or episod* or extend* or prolong* or interval* or gradual* or persist* or escalat* or deescalat* or "step* up" or "step* down" or stepup or stepdown or fail* or outcome* or admin* or schedul* or initiat* or start* or strateg* or unnecessar* or standby or "stand by")).ti,ab. 2111831
37 (("anti infectiv*" or antiinfectiv* or antibacter* or "anti bacter*" or antimicrobial* or "anti microbial*" or antibiot* or "anti biot*") adj3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or duration* or length* or short* or medium* or long* or episod* or extend* or prolong* or interval* or gradual* or persist* or escalat* or deescalat* or "step* up" or "step* down" or stepup or stepdown or fail* or outcome* or admin* or schedul* or initiat* or start* or strateg* or unnecessar* or standby or "stand by" or rescue* or misuse* or overuse* or "over use*" or overprescri* or "over prescri*" or deprescri* or abus* or steward* or resist*)).ti,ab. 243497
38 ((care* or treatment* or critical*) adj2 (pathway* or path or paths)).ti,ab. 40998
39 ((mortality* or death*) adj3 (predict* or risk* or prognos*)).ti,ab. 280800
40 ((severity* or severe* or nonsevere*) adj3 (predict* or assess* or stratif* or risk*)).ti,ab. 131734
41 or/15-40 8990005

Searches
42 14 and 41 9778
43 exp pediatrics/ or Juvenile/ or exp child/ or child health/ or infant welfare/ or Child Behavior/ or Child Welfare/ or exp child care/ or "minor (person)"/ or hospitalized child/ or hospitalized infant/ or child hospitalization/ 3297221
44 pediatric hospital/ or pediatric ward/ or pediatric intensive care unit/ 51899
45 (pediatric* or paediatric* or infan* or baby* or babies or toddler* or "pre school*" or preschool* or kindergar* or child* or minor or minors or boy* or girl* or kid or kids).ti,ab. 3358820
46 exp adolescent/ or adolescent behavior/ or adolescent health/ or exp Puberty/ or hospitalized adolescent/ 1853038
47 elementary student/ or high school student/ or middle school student/ 13476
48 ("under 18*" or "under eighteen*").ti,ab. 7795
49 (adolescen* or pubescen* or prepubescen* or puberty* or prepubert* or teen* or preteen* or juvenil* or youth* or youngster* or schoolchild* or "school age*" or schoolage* or underage* or "under age*").ti,ab. 784318
50 (young* adj1 (adult* or person* or people* or men or man or women* or woman* or male* or female* or patient* or inpatient* or outpatient*)).ti,ab. 476598
51 or/43-50 5620452
52 42 and 51 2236
53 limit 52 to english language 2007
54 (letter or editorial).pt. 2104366
55 53 not 54 1995
56 Case report/ 2969074
57 55 not 56 1602
58 nonhuman/ not human/ 5386407
59 57 not 58 1590
60 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5844635
61 59 not 60 1166
62 random:.tw. 2034866
63 placebo:.mp. 533693
64 double-blind:.tw. 249531
65 or/62-64 2316370
66 61 and 65 93
67 predict.ti. 101949
68 (validat* or rule*).ti,ab. 1362007
69 (predict* and (outcome* or risk* or model*)).ti,ab.1707981
70 ((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab. 5968590
71 decision*.ti,ab. and Statistical model/ 8131
72 (decision* and (model* or clinical*)).ti,ab. 376414
73 (prognostic* and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab. 486432
74 (stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab. 1532114
75 Receiver operating characteristic/ 222711
76 prognosis/ or prognostic assessment/ 703006

Searches		
77	or/67-76	8596281
78	61 and 77	660
79	66 or 78	705

Database name: MEDLINE ALL

Searches
1 pneumonia/ or bronchopneumonia/ or pleuropneumonia/ or pneumonia, bacterial/ or chlamydial pneumonia/ or pneumonia, mycoplasma/ or pneumonia, pneumococcal/ or pneumonia, staphylococcal/ or pneumonia, necrotizing/ or pneumonia, viral/ or organizing pneumonia/ or healthcare-associated pneumonia/ 124812
2 (pneumonia or pneumonias or bronchopneumon* or pleuropneumon*).ti,ab. 161695
3 1 or 2 231640
4 c-reactive protein/ 55385
5 (("c react*" or creact*) adj2 protein*).ti,ab. 93379
6 CRP.ti,ab. 66687
7 Procalcitonin/ 1995
8 Calcitonin/ 16297
9 (Procalcitonin* or "Pro calcitonin*" or ProCT or "Pro CT" or calcitonin1 or "calcitonin 1").ti,ab. 9697
10 (Calcitonin* adj3 (precursor* or "polypeptide alpha")).ti,ab. 170
11 (Lymphocyte Count/ or Lymphocytes/) and Neutrophils/ 10652
12 (Neutrophil* adj3 lymphocyte* adj2 (ratio or ratios or threshold or count* or relation* or relative*)).ti,ab. 14558
13 NLR.ti,ab. 14682
14 or/4-13 162232
15 3 and 14 6160
16 Respiratory Care Units/ or Respiratory Therapy Department, Hospital/ or exp Respiratory therapy/ 136128
17 hospitalization/ or hospitals/ or secondary care/ 239329
18 Emergency Service, Hospital/ or Emergency Treatment/ or Emergency Medical Services/ or exp Emergency Medicine/ or Intensive Care Units/ 224519
19 critical pathways/ or Critical Care/ 69428
20 "Referral and Consultation"/ or Triage/ or patient transfer/ or Gatekeeping/ 100863
21 Clinical Decision-Making/ or Practice Patterns, Physicians'/ 81533
22 Patient acuity/ or Patient Discharge/ or Patient Readmission/ or Retreatment/ 72647
23 Treatment Failure/ or Treatment Outcome/ 1208331
24 exp mortality/ 426038
25 Drug Administration Schedule/ or Duration of Therapy/ or Episode of Care/ or Length of Stay/ 209005
26 Inappropriate prescribing/ 4733
27 anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/ 1110784
28 (hospitaliz* or hospitalis* or rehospitalis* or rehospitaliz*).ti,ab. 357069

Searches
29 ((patient* or inpatient*) adj3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or rebound* or revisit* or declin* or worsen* or remission* or deteriorat* or escalat* or deescalat* or acuity* or triage* or triaging* or morbidit*)).ti,ab. 406221
30 ((hospital* or ICU or "intensive care*" or "intensive treatment*" or ITU or "high dependency*" or HDU or "critical care*" or "A&E" or "secondary care*" or "respiratory care*" or "accident and emergenc*") adj3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or revisit* or escalat* or deescalat* or triage* or triaging* or duration* or length* or episod*)).ti,ab. 362534
31 ((specialist* or specialized* or specialised* or emergenc* or secondary*) adj2 (care* or service* or facility* or facilities* or ward or wards or unit or units or department* or clinic or clinics) adj3 (admission* or admit* or transfer* or transition* or referral* or referred* or consultation* or consulting* or gatekeep* or postdischarg* or discharg* or retreat* or readmission* or readmit* or revisit* or escalat* or deescalat* or triage* or triaging* or duration* or length* or episod*)).ti,ab. 24230
32 ((invasive* or artificial*) adj3 (respirat* or ventilat*)).ti,ab. 21732
33 ((discharg* or referral* or referred*) adj3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or extend* or prolong* or interval* or schedul* or period*)).ti,ab. 39548
34 (hospital* adj3 ((stay* or episod*) adj3 (time* or timing* or duration* or length* or short* or medium* or long* or prolong* or extend* or period*))).ti,ab. 93047
35 ("length of stay" or "episode of care").ti,ab. 83140
36 ((therap* or intervention* or treatment*) adj3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or duration* or length* or short* or medium* or long* or episod* or extend* or prolong* or interval* or gradual* or persist* or escalat* or deescalat* or "step* up" or "step* down" or stepup or stepdown or fail* or outcome* or admin* or schedul* or initiat* or start* or strateg* or unnecessar* or standby or "stand by")).ti,ab. 1393828
37 (("anti infectiv*" or antiinfectiv* or antibacter* or "anti bacter*" or antimicrobial* or "anti microbial*" or antibiot* or "anti biot*") adj3 (decision* or appropriat* or inappropriat* or defer* or delay* or optim* or immediate* or rapid* or time* or timing* or duration* or length* or short* or medium* or long* or episod* or extend* or prolong* or interval* or gradual* or persist* or escalat* or deescalat* or "step* up" or "step* down" or stepup or stepdown or fail* or outcome* or admin* or schedul* or initiat* or start* or strateg* or unnecessar* or standby or "stand by" or rescue* or misuse* or overuse* or "over use*" or overprescri* or "over prescri*" or deprescri* or abus* or steward* or resist*)).ti,ab. 186806
38 ((care* or treatment* or critical*) adj2 (pathway* or path or paths)).ti,ab. 26381
39 ((mortality* or death*) adj3 (predict* or risk* or prognos*)).ti,ab. 180341
40 ((severity* or severe* or nonsevere*) adj3 (predict* or assess* or stratif* or risk*)).ti,ab. 84360
41 or/16-40 5172211
42 15 and 41 4346
43 exp pediatrics/ or Infant/ or Infant Health/ or Infant Welfare/ or Infant Care/ or exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ or Child Care/ or Minors/ or Child, Hospitalized/ 2502084
44 (pediatric* or paediatric* or infan* or baby* or babies or toddler* or "pre school*" or preschool* or kindergar* or child* or minor or minors or boy* or girl* or kid or kids).ti,ab. 2647692
45 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ or Puberty/ or Adolescent, Hospitalized/ 2241156

Searches
46 ("under 18*" or "under eighteen*").ti,ab. 4427
47 (adolescen* or pubescen* or prepubescen* or puberty* or prepubert* or teen* or preteen* or juvenil* or youth* or youngster* or schoolchild* or "school age*" or schoolage* or underage* or "under age*").ti,ab. 612402
48 (young* adj1 (adult* or person* or people* or men or man or women* or woman* or male* or female* or patient* or inpatient* or outpatient*)).ti,ab. 348363
49 or/43-48 5020449
50 42 and 49 1054
51 limit 50 to english language 923
52 limit 51 to (letter or historical article or comment or editorial or news or case reports) 57
53 51 not 52 866
54 Animals/ not (Animals/ and Humans/) 5164074
55 53 not 54 866
56 exp Randomized Controlled Trial/ 610842
57 randomi?ed.mp. 1106080
58 placebo.mp. 254014
59 or/56-58 1173312
60 55 and 59 63
61 predict.ti. 67313
62 (validat* or rule*).ti,ab. 972536
63 (predict* and (outcome* or risk* or model*)).ti,ab. 1214216
64 ((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab. 4314415
65 decision*.ti,ab. and Logistic models/ 5944
66 (prognostic* and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab. 314133
67 (stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab. 1136678
68 ROC curve/ 72132
69 Prognosis/ 606201
70 or/61-69 6314564
71 55 and 70 477
72 60 or 71 513

Additional search techniques

Forward citation searching

Date of search	22/02/24
How the seed papers were identified	Identified from the papers selected for this question from the search for systematic reviews; the scoping searches for this guideline; and the included papers in CG191.
Databases used	Web of Science (WOS) Core Collection (1990-present)

	• Science Citation Index Expanded (1990-present) • Social Sciences Citation Index (1990-present) • Arts & Humanities Citation Index (1990-present) • Emerging Sources Citation Index (2019-present)
Date of last update	Data updated 2024-02-19
How results were managed	Only those references that could be accessed through the NICE subscription to WOS were added to the search results. Duplicates were removed from the marked list in WOS before downloading the results.
How the results were selected	Included any papers potentially relevant to ProCT, CRP and NLR in pneumonia, in adults only. Did not make any decisions based on the location of the study. Did not include any papers about COVID-19, tuberculosis, sepsis or other conditions but did include general LRTI papers. Did not include any papers that were about methods or epidemiology. Did not include animal studies, letters or editorials. Did not include anything that was not written in English.
List of seed papers used	Baer G et al. (2013) Procalcitonin guidance to reduce antibiotic treatment of lower respiratory tract infection in children and adolescents (propaed): a randomized controlled trial. PLoS ONE, 8(8), e68419. Esposito S et al. (2011) Procalcitonin measurements for guiding antibiotic treatment in pediatric pneumonia. Respiratory Medicine, 105(12), 1939-45. Fernandes CD et al. (2019) Host inflammatory biomarkers of disease severity in pediatric community-acquired pneumonia: a systematic review and meta-analysis. Open Forum Infectious Diseases, 6(12), ofz520. Gunaratnam LC et al. (2021) Systematic review and meta-analysis of diagnostic biomarkers for pediatric pneumonia. Journal of the Pediatric Infectious Diseases Society, 10(9), 891-900.

	Tsou PY et al. (2020) Diagnostic accuracy of procalcitonin for bacterial pneumonia in children - a systematic review and meta-analysis. Infectious Diseases, 52(10), 683-697. Xiao X et al. (2015) Correlation between serum levels of c-reactive protein and infant pneumonia: a meta-analysis. Experimental & Therapeutic Medicine, 9(6), 2331-2338.
No. of results	89

Reference list checking

Date of search	22/02/24
How the seed papers were identified	Identified from the papers selected for this question from the search for systematic reviews; the scoping searches for this guideline; and the included papers in CG191.
Databases used	Web of Science (WOS) Core Collection (1990-present) • Science Citation Index Expanded (1990-present) • Social Sciences Citation Index (1990-present) • Arts & Humanities Citation Index (1990-present) Emerging Sources Citation Index (2019-present)
Date of last update	Data updated 2024-02-19
How results were managed	Only those references that could be accessed through the NICE subscription to WOS were added to the search results. Duplicates were removed from the marked list in WOS before downloading the results.
How the results were selected	Included any papers potentially relevant to ProCT, CRP and NLR in pneumonia, in adults only. Did not make any decisions based on the location of the study. Did not include any papers about COVID-19, tuberculosis, sepsis or other conditions but did include general LRTI papers. Did not include any papers that were about methods or epidemiology. Did not include animal studies, letters or editorials. Did not include anything that was not written in English.
List of seed papers used	Baer G et al. (2013) Procalcitonin guidance to reduce antibiotic treatment of lower

	respiratory tract infection in children and adolescents (propaed): a randomized controlled trial. PLoS ONE, 8(8), e68419. Fernandes CD et al. (2019) Host inflammatory biomarkers of disease severity in pediatric community-acquired pneumonia: a systematic review and meta-analysis. Open Forum Infectious Diseases, 6(12), ofz520. Gunaratnam LC et al. (2021) Systematic review and meta-analysis of diagnostic biomarkers for pediatric pneumonia. Journal of the Pediatric Infectious Diseases Societ, 10(9), 891-900. Tsou PY et al. (2020) Diagnostic accuracy of procalcitonin for bacterial pneumonia in children - a systematic review and meta-analysis. Infectious Diseases, 52(10), 683-697. Xiao X et al. (2015) Correlation between serum levels of c-reactive protein and infant pneumonia: a meta-analysis. Experimental & Therapeutic Medicine, 9(6), 2331-2338.
No. of results	90

Part 3: Cost effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Econlit	20/11/2023	Ovid	Econlit 1886 to November 11, 2023	90
Embase	20/11/2023	Ovid	Embase 1974 to 2023 November 17	2288
International HTA Database	20/11/2023	INAHTA	Version available on 20/11/23 with 21319 records	30
MEDLINE ALL	20/11/2023	Ovid	Ovid MEDLINE(R) ALL 1946 to November 17, 2023	1534

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
NHS Economic Evaluation Database (NHS EED)	20/11/2023	CRD	Archived – last updated 31 March 2015	11

Re-run results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Econlit	14/10/2024	Ovid	Econlit 1886 to October 03, 2024	6
Embase	14/10/2024	Ovid	Embase 1974 to 2024 October 11	306
International HTA Database	14/10/2024	INAHTA	Version available on 14/10/24 with 23533 records	6
MEDLINE ALL	14/10/2024	Ovid	Ovid MEDLINE(R) ALL 1946 to October 11, 2024	157

Search strategy history

Database name: Econlit

Searches		
1	(pneumonia or pneumonias or bronchopneumon* or pleuropneumon*).af.	150
2	limit 1 to yr="2014 -Current"	90
Note: in the re-run Line 2 was changed to limit 1 to yr="2023 -Current".		

Database name: Embase

Searches		
1	pneumonia/ or bilateral pneumonia/ or bronchopneumonia/ or granulomatous pneumonia/ or infectious pneumonia/ or interstitial pneumonia/ or necrotizing pneumonia/ or neonatal pneumonia/ or obstructive pneumonia/ or exp organizing pneumonia/ or bacterial pneumonia/ or community acquired pneumonia/ or health care associated pneumonia/ or hospital acquired pneumonia/ or exp lobar pneumonia/ or virus pneumonia/ or chlamydial pneumonia/ or escherichia coli pneumonia/ or haemophilus influenzae pneumonia/ or pulmonary nocardiosis/ or mycoplasma pneumonia/ or rickettsial pneumonia/ or exp staphylococcal pneumonia/ or exp streptococcus pneumonia/	314875
2	(pneumonia or pneumonias or bronchopneumon* or pleuropneumon*).ti,ab.	232562
3	1 or 2	395881

Searches
4 cost utility analysis/ 12471
5 quality adjusted life year/ 35716
6 cost*.ti. 195365
7 (cost* adj2 utilit*).tw. 12784
8 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. 385741
9 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. 66452
10 (qualit* adj2 adjust* adj2 life*).tw. 27335
11 QALY*.tw. 26801
12 (incremental* adj2 cost*).tw. 28720
13 ICER.tw. 13032
14 utilities.tw. 15135
15 markov*.tw. 40152
16 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. 72706
17 ((utility or effective*) adj2 analys*).tw. 37800
18 (willing* adj2 pay*).tw. 14735
19 (EQ5D* or EQ-5D*).tw. 26137
20 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. 5262
21 (european* adj2 quality adj3 ("5" or five)).tw. 996
22 or/4-21 635358
23 3 and 22 7788
24 afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or

Searches
vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/ 1716014
25 exp "organisation for economic co-operation and development"/ 2774
26 exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/ 3801223
27 european union/ 31487
28 developed country/ 35727
29 or/25-28 3834983
30 24 not 29 1561961
31 23 not 30 6971
32 limit 31 to english language 6647
33 (letter or editorial).pt. 2081948
34 32 not 33 6549
35 Case report/ 2939178
36 34 not 35 6182
37 nonhuman/ not human/ 5325269
38 36 not 37 6027
39 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5742113
40 38 not 39 4181
41 limit 40 to yr="2014 -Current" 2288
Note: in the re-run Line 41 was changed to limit 40 to dc=20231101-20241014.

Database name: International HTA Database

Searches
1 (pneumonia or pneumonias or bronchopneumon* or pleuropneumon*)[abs] AND (English)[Language] FROM 2014 TO 2023 15
2 (pneumonia or pneumonias or bronchopneumon* or pleuropneumon*)[Title] AND (English)[Language] FROM 2014 TO 2023 7
3 ("pneumonia"[mh] or "bronchopneumonia"[mh] or "pleuropneumonia"[mh] or "pneumonia bacterial"[mh] or "chlamydial pneumonia"[mh] or "pneumonia mycoplasma"[mh] or "pneumonia pneumococcal"[mh] or "pneumonia rickettsial"[mh] or "pneumonia staphylococcal"[mh] or "pneumonia necrotizing"[mh] or "pneumonia viral"[mh] or "organizing pneumonia"[mh] or "cryptogenic organizing pneumonia"[mh] or "healthcare-associated pneumonia"[mh]) AND (English)[Language] FROM 2014 TO 2023 21
4 1 OR 2 OR 3 30
Note: in the re-run the date was changed to FROM 2023 TO 2024.

Database name: MEDLINE ALL

Searches
1 pneumonia/ or bronchopneumonia/ or pleuropneumonia/ or pneumonia, bacterial/ or chlamydial pneumonia/ or pneumonia, mycoplasma/ or pneumonia, pneumococcal/ or pneumonia, rickettsial/ or pneumonia, staphylococcal/ or pneumonia, necrotizing/ or pneumonia, viral/ or organizing pneumonia/ or cryptogenic organizing pneumonia/ or healthcare-associated pneumonia/ 125178
2 (pneumonia or pneumonias or bronchopneumon* or pleuropneumon*).ti,ab. 159311
3 1 or 2 229286
4 Cost-Benefit Analysis/ 93463
5 Quality-Adjusted Life Years/ 15940
6 Markov Chains/ 16047
7 exp Models, Economic/ 16244
8 cost*.ti. 146284
9 (cost* adj2 utilit*).tw. 7812
10 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw.279720
11 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. 47585
12 (qualit* adj2 adjust* adj2 life*).tw. 18059
13 QALY*.tw. 14611
14 (incremental* adj2 cost*).tw. 17628
15 ICER.tw. 6134
16 utilities.tw. 9537
17 markov*.tw. 32169
18 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw.54722
19 ((utility or effective*) adj2 analys*).tw. 25292
20 (willing* adj2 pay*).tw. 9954
21 (EQ5D* or EQ-5D*).tw. 13646
22 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. 3930
23 (european* adj2 quality adj3 ("5" or five)).tw. 723
24 or/4-23 506237
25 3 and 24 3855
26 afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/

Searches
or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/ 1312779
27 "organisation for economic co-operation and development"/ 565
28 australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/ 3515662
29 european union/ 17814
30 developed countries/ 21444
31 or/27-30 3531767
32 26 not 31 1222696
33 25 not 32 3418
34 limit 33 to english language 3185
35 limit 34 to (letter or historical article or comment or editorial or news or case reports) 181
36 34 not 35 3004
37 Animals/ not (Animals/ and Humans/) 5137547
38 36 not 37 2921
39 limit 38 to yr="2014 -Current" 1534
Note: in the re-run the following lines were used:
38 36 not 37
39 limit 38 to ed=20231101-20241014
40 limit 38 to dt=20231101-20241014
41 39 or 40

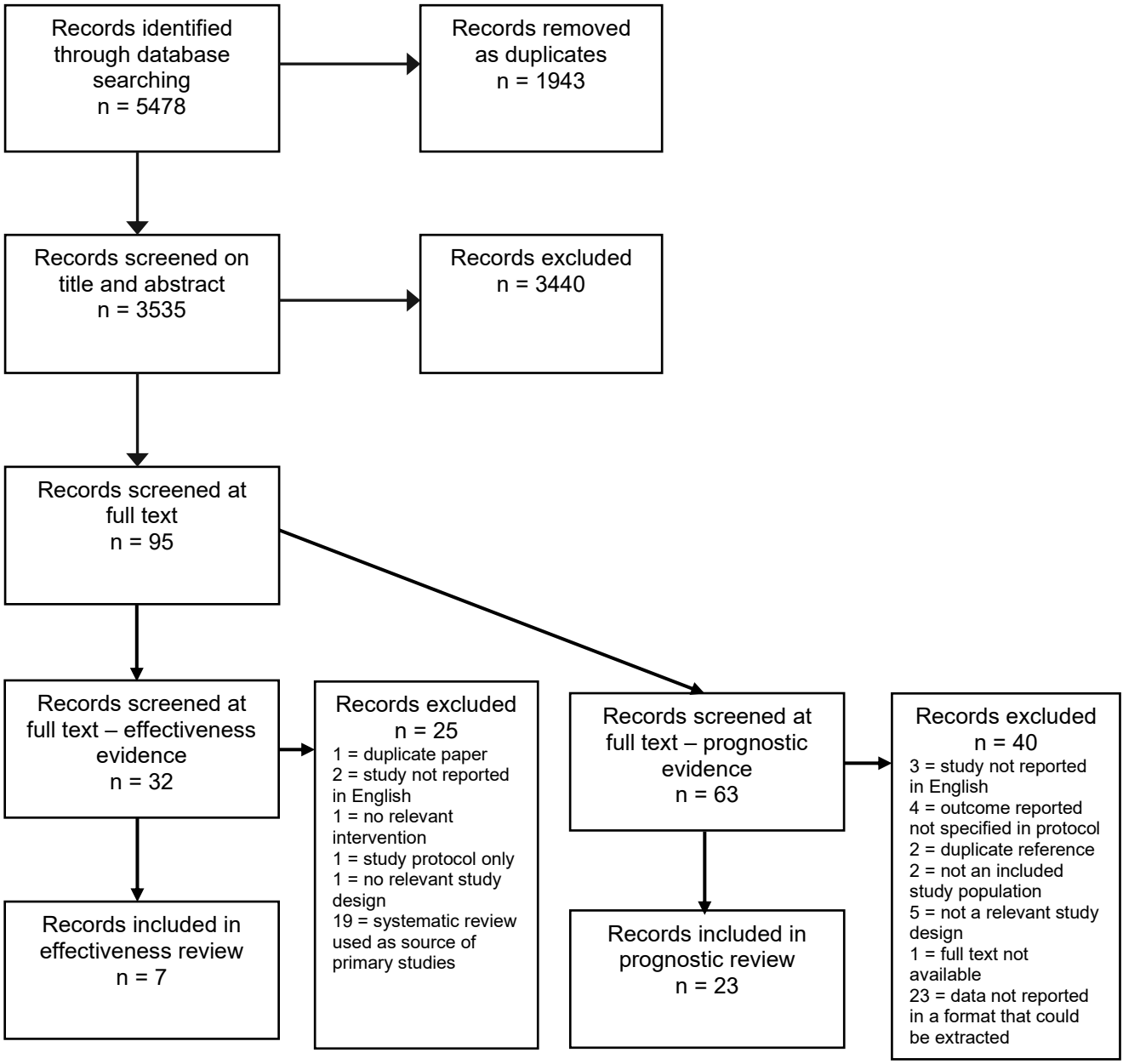
Database name: NHS Economic Evaluation Database (NHS EED)

Searches
1 MeSH DESCRIPTOR Pneumonia 252
2 MeSH DESCRIPTOR bronchopneumonia 1
3 MeSH DESCRIPTOR pleuropneumonia 0
4 MeSH DESCRIPTOR pneumonia, bacterial 90
5 MeSH DESCRIPTOR chlamydial pneumonia 0
6 MeSH DESCRIPTOR pneumonia, mycoplasma 3

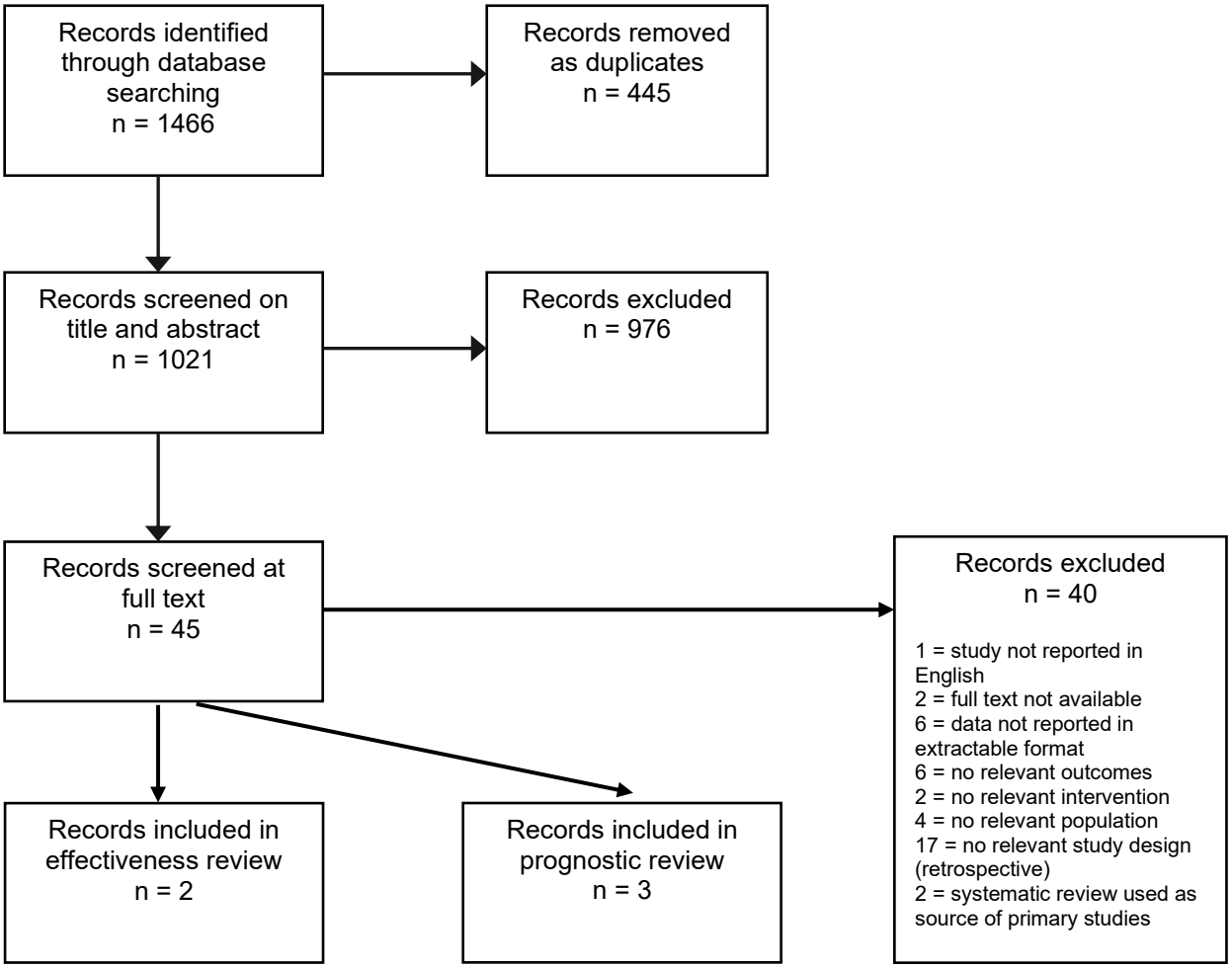
Searches
7 MeSH DESCRIPTOR pneumonia, pneumococcal 48
8 MeSH DESCRIPTOR pneumonia, rickettsial 0
9 MeSH DESCRIPTOR pneumonia, staphylococcal 10
10 MeSH DESCRIPTOR pneumonia, necrotizing 0
11 MeSH DESCRIPTOR pneumonia, viral 9
12 MeSH DESCRIPTOR Cryptogenic Organizing Pneumonia 0
13 MeSH DESCRIPTOR healthcare-associated pneumonia 0
14 (pneumonia) OR (pneumonias) 1118
15 (bronchopneumon*) OR (pleuropneumon*) 3
16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 1120
17 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15) IN NHSEED 425
18 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15) IN NHSEED FROM 2014 TO 2024 11
Note: no re-run required as the database has been archived and not updated since 31 March 2015.

Appendix C – Effectiveness and Prognostic evidence study selection

C.1 - Adults



C.2 Babies, children and young people



Appendix D – Effectiveness and Prognostic evidence

D.1 Adults

D.1.1 RCT evidence

Christ-Crain, 2006	
Bibliographic Reference	Christ-Crain, M Stolz, D Bingisser, R Muller, C Miedinger, D Huber, PR Zimmerli, W Harbarth, S Tamm, M Müller, B; Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia a Randomized trial; AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE; 2006; vol. 174 (no. 1); 84 - 93

Study details

Secondary publication of another included study- see primary study for details	**N/A**
Other publications associated with this study included in review	N/A
Trial registration number and/or trial name	The ProCAP Study: Procalcitonin-guided Reduction of the Duration of Antibiotic Therapy in Community-acquired Pneumonia. ISRCTN04176397
Study type	Randomised controlled trial (RCT)
Study location	Basel, Switzerland
Study setting	Tertiary care hospital
Study dates	November 2003 to February 2005
Sources of funding	Funding obtained from: Brahms, Pfizer, Mepha, Departments of Internal Medicine and Emergency Medicine, the Stiftung Forschung Infektionskrankheiten (SFI), and the Departments of Endocrinology and Pulmonary Medicine, University Hospital Basel, Switzerland.
Inclusion criteria	Adult patients (>18 years) with CAP as the principle diagnosis on admission CAP defined as a new infiltrate on chest radiograph and the presence of one or several of the following acute respiratory signs or symptoms: cough, sputum production, dyspnea, core body

	temperature exceeding 38.0 °C, auscultatory findings of abnormal breath sounds and rales
Exclusion criteria	Patients with cystic fibrosis Patients with active pulmonary tuberculosis Patients with hospital acquired pneumonia (HAP) Severely immunocompromised patients
Intervention(s)	Antibiotic treatment was guided by serum procalcitonin levels, whereby patients were classified into 4 groups using cut-offs derived in a previous study. The following algorithm was used: - A procalcitonin level of less than 0.1 µg/L suggested absence of bacterial infection and the initiation or continuation of antibiotics was *strongly discouraged* - A procalcitonin level between 0.1 µg/L and 0.25 µg/L suggested a bacterial infection was unlikely, and the initiation or continuation of antibiotics was *discouraged* - A procalcitonin level from 0.25 µg/L to 0.5 µg/L was considered to indicate a possible bacterial infection and the initiation or continuation of antibiotics was *encouraged* - A procalcitonin level greater than 0.5 µg/L strongly suggested the presence of bacterial infection and antibiotic treatment and continuation was *strongly encouraged.* Re-evaluation of the clinical status and measurement of serum procalcitonin levels was recommended after 6-24 hours in all patients from whom antibiotics were withheld. Procalcitonin levels were reassessed after 4, 6 and 8 days. Antibiotics were discontinued on the basis of the procalcitonin cut-offs defined above. In patients with very high procalcitonin levels on admission (greater than 10 µg/L), discontinuation of antibiotics was encouraged if levels decreased to less than 10% of the the initial value (e.g., 1 µg/L instead of 0.25 µg/L).
Comparator	Antibiotic therapy was chosen on the basis of usual practice guidelines.
Outcome measures	Total antibiotic use - antibiotic prescription Total antibiotic use - duration Clinical cure (defined as resolution of clinical, laboratory and radiographic signs of CAP)

	Clinical improvement (defined as reduction of clinical signs and symptoms, improvement of laboratory findings, and reduction of the number or intensity of radiographic signs) Treatment failure (death, recurrence, relapse, persistence of clinical, laboratory and radiologic signs of CAP, and patients lost to follow-up) All-cause mortality
Number of participants	N = 302 (n = 151 PCT group; n = 151 control group)
Duration of follow-up	Primary and secondary outcomes were reported on days 4, 6, and 8, and at 6-week follow-up.
Loss to follow-up	In the procalcitonin group (n=151), 18 patients died and 2 were lost to follow-up In the control group (n=151), 20 patients died and no patients were lost to follow-up. All 302 patients were included in ITT analyses.
Methods of analysis	Discrete variables are expressed as counts (percentage) and continuous variables as means +/- SD. Endpoints were pre-defined and analysed on the basis of intention to treat. Comparability of the control and PCT group was analysed by Chi-squared test and non-parametric Mann-Whitney U test. Time to discontinuation of antibiotic treatment was compared between the 2 groups by use of log-rank test. Cox proportional hazards regression analysis was used to estimate the rate of antibiotic treatment discontinuation, after adjustment for PSI class.
Additional comments	Baseline characteristics on admission were similar in both groups. 87% of patients had relevant comorbidities. The median duration of antibiotic therapy of 13 days in the control group appears rather long, as guidelines recommend a duration in CAP of 7-10 days (at the time of this study publication). Authors argue they aimed to mirror usual care in the control group, and held that physicians tend to over treat patients, especially those who are severely unwell and required admission to hospital, so 10-14 days is often the usual length of treatment for these patients.

CAP: community acquired pneumonia; ITT: intention to treat; N/A: not applicable; PCT: procalcitonin; PSI: pneumonia severity index; SD: standard deviation

Characteristics

Arm-level characteristics

Characteristic	Procalcitonin group (N = 151)	Control group (N = 151)
% Female No of events	n = 57 ; % = 38	n = 58 ; % = 38
Age (SD) Mean (SD)	70 (17)	70 (17)
Smoking status Current smoker No of events	n = 34 ; % = 23	n = 39 ; % = 26
Smoking history (Number of years smoked) Mean (SD)	42 (27)	38 (20)
Coronary artery disease No of events	n = 49 ; % = 33	n = 48 ; % = 32
Hypertensive heart disease No of events	n = 42 ; % = 28	n = 36 ; % = 24
Congestive heart failure No of events	n = 7 ; % = 5	n = 9 ; % = 6
Peripheral vascular disease No of events	n = 11 ; % = 7	n = 9 ; % = 6
Cerebrovascular disease No of events	n = 8 ; % = 5	n = 8 ; % = 5
Renal dysfunction No of events	n = 36 ; % = 24	n = 45 ; % = 30
Liver disease No of events	n = 12 ; % = 8	n = 19 ; % = 13
Diabetes mellitus No of events	n = 32 ; % = 21	n = 29 ; % = 19
COPD No of events	n = 44 ; % = 29	n = 32 ; % = 21
Neoplastic disease	n = 25 ; % = 17	n = 23 ; % = 15

Characteristic	Procalcitonin group (N = 151)	Control group (N = 151)
No of events		
PSI class I, II, and III No of events	n = 54 ; % = 36	n = 66 ; % = 44
PSI class IV No of events	n = 68 ; % = 45	n = 62 ; % = 41
PSI class V No of events	n = 29 ; % = 19	n = 23 ; % = 15

COPD: chronic obstructive pulmonary disease; PSI: pneumonia severity index; SD: standard deviation

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Gavazzi, 2022

Bibliographic Reference	Gavazzi, Gaetan; Drevet, Sabine; Debray, Matthieu; Bosson, Jean Luc; Tidadini, Fatah; Paccalin, Marc; de Wazieres, Benoit; Celarier, Thomas; Bonnefoy, Marc; Vitrat, Virginie; Procalcitonin to reduce exposure to antibiotics and individualise treatment in hospitalised old patients with pneumonia: a randomised study.; BMC geriatrics; 2022; vol. 22 (no. 1); 965

Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A

Trial registration number and/or trial name	PROPAGE study (*PROcalcitonine chez les Patients AGEs)*. This trial is registered in ClinicalTrials.gov NCT02173613
Study type	Randomised controlled trial (RCT)
Study location	France
Study setting	8 geriatric units at 6 French hospitals
Study dates	December 2013 to June 2016
Sources of funding	The work was supported by Thermo Fisher Scientific and a grant from Programme Hospitalier de Recherche Clinique, French Ministry of Health (PHRC). BioMérieux help in organisation of the study with biologists.
Inclusion criteria	Elderly patients ≥ 80 years of age Diagnosis of pneumonia, defined by the presence of at least 2 clinical signs of pneumonia and based on the results of X-ray or scan. Antibiotic treatment for pneumonia had been initiated in the previous 48 hours
Exclusion criteria	Severely immunocompromised patients Patients who had an infection due to a virus, parasite, Listeria spp., Legionella pneumophilia, or Mycobacterium tuberculosis Patients who had an associated endovascular or chronic infection, or a lung abscess upon admission Patients under palliative care Patients who died within 24 hours of admission Patients receiving antibiotics for a chronic infection
Intervention(s)	Patients assigned to the PCT group received an antibiotic regimen that was terminated early according to clinical evaluation algorithms guided by PCT levels. Physicians were instructed on the use of these algorithms prior to study initiation. <u>Algorithm 1 (for use on Day 2)</u> - If PCT values for Day 0 and Day 2 < 0.25 ng/mL, stop antibiotics recommended

	- If PCT values for Day 0 and/or Day 2 > 0.25 ng/mL, continue antibiotics for 2 days then assess PCT at Day 4 (and apply algorithm 2) <u>Algorithm 2 (for use on Days 4, 6 and 8)</u> - If previous PCT value < 0.25 ng/mL, and patient is stable and has PCT < 0.1 ng/mL, *strongly recommend* stopping antibiotics - If previous PCT value < 0.25 ng/mL, and patient is stable and has PCT > 0.1 ng/mL and < 0.25 ng/mL, *recommend* stopping antibiotics - If previous PCT value > 0.25 ng/mL and < 10 ng/mL, and patient is stable and PCT < 0.25 ng/mL, *recommend* stopping antibiotics - If previous PCT value > 10 ng/mL, and patient is stable and PCT has decreased by >90%, *recommend* stopping antibiotics
Comparator	Patients assigned to the Control group received a conventional antibiotic regimen that was terminated according to the treating physician's discretion and were managed per usual treatment strategies according to the recommendations from the French Infectious Diseases Society (SPILF). PCT measurements on Days 2, 4, 6 and 8 were also performed.
Outcome measures	Total antibiotic use - duration Mortality Adverse events, including death, hospitalisation, prolonging of existing hospitalisation, or leading to permanent or significant disability/incapacity. Recovery rate on day 45 - defined as recovered if, according to physician judgement, no clinical sign of pneumonia persisted.
Number of participants	N = 107 (n=50 PCT group; n=57 control group)
Duration of follow-up	Procalcitonin assessed on days 2, 4, 6 and 8. Patients were followed-up via telephone interviews at 6 weeks.
Loss to follow-up	N = 107 patients were recruited and randomised. All 107 patients completed the 6 week follow-up and were included in the ITT population. 24 patients did not comply with the PCT-based algorithm (compliance in PCT group was 52%), so the per-protocol population included n=83 patients: 26 in the PCT group and 57 in the control group. (Likely due to overruling of the algorithm by the clinician).

Methods of analysis	A descriptive statistical analysis at baseline was performed for all collected variables and results were reported as mean (standard deviation, SD) or median (interquartile ranges, IQR) if appropriate for continuous variables, and count (percentage, %) for qualitative variables. Usual parametric and non-parametric tests were used for group comparisons. The main analysis was performed on the intention-to-treat (ITT) population. A secondary analysis was performed on the per protocol (PP) population.
Additional comments	The population in this study was very old (≥ 80 years), disabled, vulnerable, with poor nutritional status or at risk of malnutrition. As expected, most of the population exhibited impaired cognitive function, declined functional status, high pneumonia severity scores, and respiratory decompensation upon their presentation. Baseline PCT levels (ng/mL): PCT group = 2.6 (6.70); control group = 4.84 (12.73); *p = 0.25.* Although not significantly different, it does indicate a degree of difference in baseline PCT levels which may have impacted implementation of the PCT algorithm.

ITT: intention to treat; N/A: not applicable; PCT: procalcitonin

Characteristics

Arm-level characteristics

Characteristic	Procalcitonin group (N = 50)	Control group (N = 57)
% Female No of events	n = 25 ; % = 50	n = 29 ; % = 50.9
Age (SD) Mean (SD)	88 (5.1)	87.6 (5)
Smoking status No of events	n = 2 ; % = 4.1	n = 2 ; % = 3.6
Own home No of events	n = 39 ; % = 79.6	n = 44 ; % = 77.2
Nursing home No of events	n = 10 ; % = 20.4	n = 13 ; % = 22.8
PSI class III No of events	n = 8 ; % = 16	n = 12 ; % = 21
PSI class IV No of events	n = 35 ; % = 70	n = 28 ; % = 49.1
PSI class V	n = 7 ; % = 14	n = 17 ; % = 29.8

Characteristic	Procalcitonin group (N = 50)	Control group (N = 57)
No of events		

PSI: pneumonia severity index; SD: standard deviation

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(24/50 intervention group patients did not adhere to the PCT algorithm. Reasons for non-adherence are not provided (e.g., clinician overruling; patient choice), but ITT and per-protocol analyses produce similar findings. No information on blinding of outcome assessors, and outcome interviews were conducted by the study team.)*
Overall bias and Directness	Overall Directness	Partially applicable *(Patients were all >80 years)*

Montassier, 2019

Bibliographic Reference Montassier, Emmanuel; Javaudin, Francois; Moustafa, Fares; Nandjou, Demeno; Maignan, Maxime; Hardouin, Jean-Benoit; Annoot, Caroline; Ogielska, Maja; Orer, Pascal-Louis; Schotte, Thibault; Bouget, Jacques; Agha Babaei, Syamak; Raynal, Pierre-Alexis; Eche, Antoine; Duc, Albert Trinh; Cojocaru, Ruxandra-Aimee; Benaouicha, Nesrine; Potel, Gilles; Batard, Eric; Talan, David A; Guideline-Based Clinical Assessment Versus Procalcitonin-Guided Antibiotic Use in Pneumonia: A Pragmatic Randomized Trial.; Annals of emergency medicine; 2019; vol. 74 (no. 4); 580-591

Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A

Trial registration number and/or trial name	Trial registration number: NCT01723644
Study type	Randomised controlled trial (RCT)
Study location	France
Study setting	Emergency Departments at 12 French hospitals
Study dates	November 2012 to April 2015
Sources of funding	The study was supported by a grant from the French Ministry of Health (PHRC API12/N/080).
Inclusion criteria	Adult patients attending ED with a presumptive diagnosis of CAP. Criteria for diagnosis were patients with at least 2 of 3 respiratory infection criteria: an acute respiratory symptom (cough, sputum production, dyspnea, tachypnea, or pleuritic pain); abnormal lung auscultatory sounds; and signs of infection (e.g., temperature >38.0, sweats, chills), and a new infiltrate on chest radiograph.
Exclusion criteria	Severely immunocompromised patients Patients with life threatening comorbidities leading to possible imminent death Pregnant patients Patients with an exacerbation of COPD Patients who had received antibiotics for the current episode of illness Patients who were expected to be discharged from the ED within 6 hours (because the protocol required repeated assessment at 6 to 24 hours).
Intervention(s)	In the 3 months before the beginning of the trial, all physicians in the ED and hospital received approximately 2 hours of training about the background and use of guideline-directed clinical assessment and the procalcitonin algorithm. The procalcitonin algorithm was based on that used in previous studies and was as follows: - If procalcitonin level was less than 0.1 mg/L, initiation of antibiotics was strongly not recommended - If procalcitonin level was less than or equal to 0.25 mg/L, initiation of antibiotics was not recommended

	- If procalcitonin level was greater than 0.25 mg/L, initiation of antibiotics was recommended, - If procalcitonin level was greater than 0.5 mg/L, initiation of antibiotics was strongly recommended. If antibiotics were not initiated in the ED after the first procalcitonin result, procalcitonin measurements were repeated after 6 to 24 hours, and initiation of antibiotics was evaluated with the same cut-off ranges. Among hospitalized participants treated with antibiotics, procalcitonin measurements were repeated on days 3, 5, and 7, and antibiotic continuation or discontinuation was recommended or not recommended according to the same criteria above. Prespecified allowed exceptions to the procalcitonin algorithm included immediate need for ICU admission, respiratory or hemodynamic instability, and severe community-acquired pneumonia (Pneumonia Severity Index class IV or V). However, the procalcitonin algorithm was a guideline that could be overruled by the treating physician according to his or her judgment.
Comparator	Participants in the clinical assessment (control) group were evaluated 6 to 24 hours after randomization—but in this case, clinically—for continuation or discontinuation of antibiotics started in the ED. The clinical assessment strategy was as follows: Participants receiving a diagnosis of community-acquired pneumonia in the ED were prescribed antibiotic treatment by their treating emergency physician, then were reassessed 6 to 24 hours after randomization by a different attending hospital physician to confirm or invalidate the diagnosis of community-acquired pneumonia and need to continue antibiotics. If the diagnosis of community-acquired pneumonia was not confirmed, then antibiotic discontinuation was recommended; if another infection requiring antibiotic treatment was diagnosed, then antibiotic continuation was recommended. The second intervention occurred on day 5, when hospitalized participants were evaluated by the treating hospital physician using clinical stability criteria based on IDSA/ATS guidelines to stop antibiotic treatment as follows: - If the participant was afebrile for 48 to 72 hours and had no more than 1 community acquired pneumonia–associated sign of clinical - Instability (i.e., pulse rate >100 beats/min, respiratory rate >24 breaths/min, systolic blood pressure <90 mm Hg, SaO2 <90%, or PO2 <60 mm Hg on room air), then discontinuation of antibiotics was strongly recommended.

	- If the patient did not fulfil these criteria, then continuation of antibiotics was recommended for 2 more days, and then the patient was re-evaluated.
Outcome measures	Clinical cure (defined as resolution of clinical, laboratory and radiographic signs of CAP) Composite of overall adverse outcomes occurring within 30 days of ED admission. It included death from any cause, ICU admission for any reason, disease-specific complications (i.e., persistence or development of pneumonia, lung abscess, empyema, and acute respiratory distress syndrome), and recurrence of LRTI in need of antibiotics with or without hospital readmission Total days of antibiotic exposure within 30 days after ED admission Proportion of patients treated with antibiotics for less than or equal to 5 days Adherence to procalcitonin algorithm and clinical reassessment protocols
Number of participants	N = 285 (n=142 procalcitonin group; n=143 control group) Modified intention-to-treat group included n=131 in both groups (patients who received antibiotics for diagnoses other than community-acquired pneumonia or who were found to have Legionnaires' disease were excluded. If patients were misdiagnosed with CAP in ED and actually had another infection, the procalcitonin and clinical assessment strategy would not be applicable, especially where longer durations of antibiotics are required or procalcitonin would not be used).
Duration of follow-up	30 days
Loss to follow-up	370 patients with CAP presenting to EDs were assessed for eligibility; n=85 were not eligible (74 met exclusion criteria, 8 refused participation, 3 gave other reasons) so n=285 were randomised. 23 were excluded from the modified ITT analysis, mainly because they received antibiotics for another indication than CAP, because they had Legionnaires' disease, or because an enrolment error meant they met exclusion criteria. Final sample = 262 (n=131 in each group)
Methods of analysis	Results are given as medians and interquartile ranges (IQRs) for continuous variables and as frequencies and percentages for categoric variables. Mann-Whitney tests were used for continuous variables. We provide a P value for the primary outcome analysis and 95% confidence intervals (CIs) of the difference for other outcome comparisons. The proportion of patients with antibiotic treatment within the 30-day follow-up period was described with Kaplan-Meier curves and compared with the log-rank test.

ATS: American Thoracic Society; CAP: community acquired pneumonia; COPD: chronic obstructive pulmonary disease; ED: emergency department; ICU: intensive care unit; IDSA: Infectious Diseases Society of America; ITT: intention to treat; LRTI: lower respiratory tract infection; N/A: not applicable

Characteristics

Arm-level characteristics

Characteristic	Procalcitonin group (N = 142)	Control group (N = 143)
% Female No of events	n = 62 ; % = 44	n = 54 ; % = 38
Age (SD) Median (IQR)	67 (46 to 83)	67 (47 to 81)
Smoking status Past and current smoking No of events	n = 51 ; % = 36	n = 45 ; % = 31
Coronary heart disease No of events	n = 19 ; % = 13	n = 16 ; % = 11
Cerebrovascular disease No of events	n = 4 ; % = 3	n = 4 ; % = 3
Renal dysfunction No of events	n = 7 ; % = 5	n = 2 ; % = 1
COPD No of events	n = 11 ; % = 8	n = 16 ; % = 11
Neoplastic disease No of events	n = 7 ; % = 5	n = 8 ; % = 6
Diabetes No of events	n = 27 ; % = 19	n = 35 ; % = 24
PSI class III No of events	n = 54 ; % = 38	n = 56 ; % = 39
PSI class III No of events	n = 27 ; % = 19	n = 33 ; % = 23
PSI class IV No of events	n = 49 ; % = 35	n = 47 ; % = 33

Characteristic	Procalcitonin group (N = 142)	Control group (N = 143)
PSI class V No of events	n = 12 ; % = 8	n = 7 ; % = 5
Hospitalised within 24 hours No of events	n = 126 ; % = 80	n = 114 ; % = 88

COPD: chronic obstructive pulmonary disease; IQR: interquartile range; PSI: pneumonia severity index; SD: standard deviation

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(24% of patients did not adhere to the PCT algorithm; ITT analyses used; no information on blinding of outcome assessors.)*
Overall bias and Directness	Overall Directness	Directly applicable

ITT: intention to treat; PCT: procalcitonin

Schuetz, 2009

Bibliographic Reference	Schuetz P; Christ-Crain M; Thomann R; Falconnier C; Wolbers M; Widmer I; Neidert S; Fricker T; Blum C; Schild U; Regez K; Schoenenberger R; Henzen C; Bregenzer T; Hoess C; Krause M; Bucher HC; Zimmerli W; Mueller B; ; Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial.; JAMA; 2009; vol. 302 (no. 10)

Study details

Secondary publication of another included study- see primary study for details	N/A Note that this study was of all patients with a primary diagnosis of LRTI but subgroup analyses are presented for patients with CAP. The data extracted here for the current review is from the sub-sample with CAP only.
Other publications associated with this study	N/A

included in review	
Trial registration number and/or trial name	The ProHOSP Trial isrctn.org Identifier: ISRCTN95122877
Study type	Randomised controlled trial (RCT)
Study location	Switzerland
Study setting	Emergency departments of tertiary care hospitals
Study dates	October 2006 to March 2008
Sources of funding	Swiss National Science Foundation, Sante´ Suisse, Gottfried and Julia Bangerter-Rhyner-Foundation, the University Hospital Basel, the Medical University Clinic Liestal, the Medical Clinic Buergerspital Solothurn, the Cantonal Hospitals Muensterlingen, Aarau, and Lucerne, respectively, the Swiss Society for Internal Medicine, and the Department of Endocrinology, Diabetology, and Clinical Nutrition, University Hospital Basel.
Inclusion criteria	Patients at least 18 years old and admitted from the community or a nursing home with acute LRTI of less than 28 days duration Inclusion criteria for LRTI were presence of at least 1 respiratory symptom (cough, sputum production, dyspnea, tachypnea, pleuritic pain), plus at least 1 finding during auscultation (rales, crepitation), or 1 sign of infection (body temp >38 °C, shivering or leukocyte count >10 000/μL or <4000/μL). Plus for CAP diagnosis there had to be a new infiltrate on chest radiograph
Exclusion criteria	Patients with hospital acquired pneumonia (HAP) Severely immunocompromised patients Patients receiving antibiotics for a chronic infection Patients unable to give informed consent due to language restriction or severe dementia Patients with active intravenous drug use Patients with life threatening comorbidities leading to possible imminent death
Intervention(s)	In the PCT group, PCT levels were communicated via a website to the treating physician, together with a treatment recommendation for antibiotics based on the PCT algorithm validated in previous studies. PCT Algorithm:

	- If PCT was less than 0.1 µg/L, initiation or continuation of antibiotics was *strongly discouraged* - If PCT was less than 0.25 µg/L, initiation or continuation of antibiotics was *discouraged* - If PCT was higher than 0.25 µg/L, initiation or continuation of antibiotics was *encouraged* - If PCT was higher than 0.5 µg/L, initiation or continuation of antibiotics was *strongly encouraged* - In patients with high PCT values on admission (> 10 µg/L), if PCT levels decreased by 80%, stopping antibiotics was *recommended*, and if PCT levels decreased by 90%, stopping antibiotics was *strongly recommended*. If antibiotics were withheld, hospitalised patients were clinically re-evaluated and PCT measurements repeated after 6-24 hours. PCT measurements were repeated after 3, 5 and 7 days and antibiotic treatment was continued or discontinued used the same cut-off ranges. Overruling of the PCT algorithm was possible by prespecified criteria, namely in patients with immediate need for intensive care unit (ICU) admission, with respiratory or hemodynamic instability, with positive antigen test for Legionella pneumophila, or after consulting with the study centre.
Comparator	In the control group, antibiotic use was in accordance with recommendations from up-to-date guidelines. In brief, antibiotic use was encouraged in CAP for 5 to 10 days in uncomplicated cases, at least 14 days in L pneumophila CAP, at least 10 days in necrotizing CAP, and in the case of empyema or lung abscess, where drainage was suggested.
Outcome measures	Composite of overall adverse outcomes occurring within 30 days of ED admission. It included death from any cause, ICU admission for any reason, disease-specific complications (i.e., persistence or development of pneumonia, lung abscess, empyema, and acute respiratory distress syndrome), and recurrence of LRTI in need of antibiotics with or without hospital readmission Antibiotic exposure (including duration of IV and oral antibiotic therapy) Adverse effects of antibiotic treatment Length of hospital stay

Number of participants	Overall study sample = 1359 (PCT group n=671; Control group n = 688). CAP only sub-sample = 925 (PCT group n=460; Control group n = 465).
Duration of follow-up	30 days
Loss to follow-up	22 patients (16 PCT group and 6 control) withdrew their informed consent so were excluded from analyses.
Methods of analysis	The primary analysis population is the full analysis set, which includes all randomized patients following an intention-to-treat principle. A confidence interval (CI) for the difference of the overall adverse outcome rates was calculated based on Cochran statistic using Mantel-Haenszel weights and stratification by type of LRTI.
Additional comments	The intervention with PCT testing and physicians' gained experience of reduced antibiotic treatment may have affected antibiotic prescription patterns in the control group (spillover effect).

CAP: community acquired pneumonia; ED: emergency department; LRTI: lower respiratory tract infection; N/A: not applicable; PCT: procalcitonin

Characteristics

Arm-level characteristics

Characteristic	Procalcitonin group (N = 671)	Control group (N = 688)
% Female No of events	n = 269 ; % = 40.1	n = 308 ; % = 44.8
Age (SD) Median (IQR)	73 (59 to 82)	72 (59 to 82)
Coronary heart disease No of events	n = 146 ; % = 21.8	n = 136 ; % = 19.8
Cerebrovascular disease No of events	n = 54 ; % = 8.1	n = 56 ; % = 8.1
Renal dysfunction No of events	n = 156 ; % = 23.3	n = 146 ; % = 21.2
COPD No of events	n = 265 ; % = 39.5	n = 268 ; % = 39

Characteristic	Procalcitonin group (N = 671)	Control group (N = 688)
Neoplastic disease No of events	n = 69 ; % = 10.3	n = 98 ; % = 14.2
Diabetes No of events	n = 118 ; % = 17	n = 113 ; % = 16.4
PSI class I No of events	n = 76 ; % = 11	n = 63 ; % = 9.3
PSI class II No of events	n = 138 ; % = 20.1	n = 124 ; % = 18.4
PSI class III No of events	n = 147 ; % = 21.4	n = 152 ; % = 22.7
PSI class IV No of events	n = 243 ; % = 35.3	n = 252 ; % = 37.6
PSI class V No of events	n = 84 ; % = 12.2	n = 80 ; % = 11.9
Hospitalised patients No of events	n = 628 ; % = 93.7	n = 629 ; % = 91.4
Outpatients No of events	n = 43 ; % = 6.4	n = 59 ; % = 8.6

COPD: chronic obstructive pulmonary disease; IQR: interquartile range; PSI: pneumonia severity index; SD: standard deviation

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable *(Main study sample is all patients with LRTI, but subgroup results presented for CAP only patients.)*

CAP: community acquired pneumonia; LRTI: lower respiratory tract infection

D.1.2 Non-randomised control evidence

Akagi, 2019	
Bibliographic Reference	Akagi, Takanori; Nagata, Nobuhiko; Wakamatsu, Kentaro; Harada, Taishi; Miyazaki, Hiroyuki; Takeda, Satoshi; Ushijima, Shinichiro; Aoyama, Takashi; Yoshida, Yuji; Yatsugi, Hiroshi; Wada, Kenji; Ueda, Yusuke; Fujita, Masaki; Watanabe, Kentaro; Procalcitonin-Guided Antibiotic Discontinuation Might Shorten the Duration of Antibiotic Treatment Without Increasing Pneumonia Recurrence.; The American journal of the medical sciences; 2019; vol. 358 (no. 1); 33-44

Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial registration number and/or trial name	Not reported
Study type	Case-control study
Study location	Japan
Study setting	Hospital
Study dates	Prospective cohort (PCT group): October 2014 to December 2017 Retrospective cohort (control group): October 2010 to September 2014
Sources of funding	Paper states: None
Inclusion criteria	Hospitalised patients with CAP or HCAP (healthcare associated pneumonia) Pneumonia criteria were: (1) onset outside the hospital, (2) acute illness with symptoms including new cough with or without sputum, fever or chills, pleuritic chest pain, or dyspnea, (3) chest X-ray

	showing an opacity compatible with the presence of acute pneumonia and (4) PCT levels >0.20 ng/mL on admission.
Exclusion criteria	Patients with aspiration pneumonia Patients with dementia
Intervention(s)	In the PCT-guided antibiotic discontinuation group, PCT levels were measured on days 5 (+/-1 day), 8 (+/-1 day) and 11 (+/-1 day) and every 3 days thereafter if needed. Physicians in charge of treatment were encouraged to discontinue antibiotics when PCT levels decreased to <0.20 ng/mL; discontinuation was strongly encouraged at levels below 0.10 ng/mL.
Comparator	The historical controls were patients admitted in the period before PCT was introduced in clinical practice; during these periods, PCT was measured mainly on admission for the assessment of pathogen involved (bacterial or not) and severity of pneumonia, and not used to determine antibiotic discontinuation. For usual care in Japan, antibiotics are discontinued when patients meet all (or all but one) of the following criteria: (1) body temperature <37.0°C, (2) normalization of WBC count, (3) improvement in CRP to less than 30% of peak levels and (4) apparent improvement of pneumonic shadows in chest X-ray images
Outcome measures	Total antibiotic use - duration Mortality Adverse event: recurrence of pneumonia during admission Rehospitalisation due to pneumonia recurrence
Number of participants	N = 232 (n= 116 patients in each group)
Duration of follow-up	30 days
Loss to follow-up	Not reported
Methods of analysis	Comparisons of variables between the PCT-guided group and the control group were performed with the Mann-Whitney U test. Factors related to duration of antibiotic treatment were examined with multivariable linear regression analysis.
Additional comments	Median duration of antibiotic treatment was 8 days, which is still longer than the 5 days suggested by some guidelines for the antibiotic treatment of CAP. However, this study included many elderly, moderate and severe pneumonia and HCAP patients with high baseline PCT levels. Therefore, duration of antibiotic treatment might be lengthened in the present study. The same antibiotics were used during the study period and the historical control period. These antibiotics were chosen according

	to JRS guidelines; therefore, it is unlikely that how antibiotics were selected affected the results of the present study.

CAP: community acquired pneumonia; CRP: C-reactive protein; HCAP: healthcare associated pneumonia; PCT: procalcitonin; N/A: not applicable; WBC: white blood cells

Characteristics

Arm-level characteristics

Characteristic	Procalcitonin group (N = 116)	Control group (N = 116)
% Female No of events	n = 49 ; % = 42.2	n = 40 ; % = 34.5
Age (SD) Median (IQR)	78 (70 to 85)	79 (73 to 85)
Chronic lung disease No of events	n = 57	n = 35
Diabetes mellitus No of events	n = 24	n = 28
Cerebrovascular disease No of events	n = 4	n = 14
Chronic heart failure No of events	n = 9	n = 9
Kidney disease No of events	n = 4	n = 2
Malignancy No of events	n = 6	n = 8
Liver disease No of events	n = 2	n = 2
CAP No of events	n = 93 ; % = 80.2	n = 83 ; % = 71.6
HCAP No of events	n = 23 ; % = 19.8	n = 33 ; % = 28.4
PSI class I	n = 5 ; % = 4.3	n = 3 ; % = 2.6

No of events		
PSI class II No of events	n = 24 ; % = 20.7	n = 9 ; % = 7.8
PSI class III No of events	n = 25 ; % = 21.5	n = 36 ; % = 31
PSI class IV No of events	n = 53 ; % = 45.7	n = 56 ; % = 48.3
PSI class V No of events	n = 9 ; % = 7.8	n = 12 ; % = 10.3
Baseline PCT Median (IQR)	0.76 (0.33 to 2.72)	1.03 (0.4 to 4.27)

CAP: community acquired pneumonia; HCAP: healthcare associated pneumonia; IQR: interquartile range; PSI: pneumonia severity index

Critical appraisal - CASP checklist for case-control studies

Overall risk of bias	Moderate: baseline PCT levels were noticably high and the population included quite elderly patients with severe illness.
Overall directness	Directly applicable

Subedi, 2020

Bibliographic Reference	Subedi, Bibidh; Louzon, Patricia; Zappas, Kristie; Onyia, Wilfred; DeBoer, Kevin; Impact of Pharmacist-Led Procalcitonin-Guided Antibiotic Therapy in Critically Ill Patients With Pneumonia.; Hospital pharmacy; 2020; vol. 55 (no. 3); 204-210

Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this	N/A

study included in review	
Trial registration number and/or trial name	Trial not registered
Study type	Case-control study
Study location	United States
Study setting	Intensive care units
Study dates	Prospective cohort: 25th Feb 2017 to 12th July 2017 Historical cohort: 1st Aug 2016 to 24th Feb 2017
Sources of funding	The author(s) received no financial support for the research, authorship, and/or publication of this article.
Inclusion criteria	Adult patients (>18 years) with the diagnosis of pneumonia and admitted to the ICU Diagnosis of CAP was defined as the presence of clinical features (i.e. cough, fever, sputum production, or pleuritic chest pain) and evidence of infiltrates on chest radiograph. VAP and HAP were defined as pneumonia that occurs with new lung infiltrate plus clinical features such as new-onset fever (temperature >100.4 °F), purulent sputum, leukocytosis defined by white blood cells (WBC) >10 000/μL, and decline in oxygenation (O 2 saturation <90%), where VAP occurs >48 hours after endotracheal intubation and HAP occurs ≥48 hours after hospital admission
Exclusion criteria	Patients with cystic fibrosis Severely immunocompromised patients Pregnant patients Patients with pancreatitis Patients scheduled for surgery or had undergone surgery in the past 14 days Patients diagnosed with septic shock Patients diagnosed with a concomitant bacterial infection in addition to pneumonia at the time of antibiotic initiation

	Patients in the historical cohort were also excluded if they had 2 or more consecutive PCT levels ordered within 24 to 48 hours following antibiotic initiation to prevent inclusion of patients who may have had influence of PCT algorithm in their infection management
Intervention(s)	In the prospective cohort, clinical pharmacists contacted the prescribing providers and requested an order for a baseline PCT level within 24 hours of initiating antibiotics and a repeat 24- to 48-hour PCT level. Based on the 2 serial PCT levels, clinical pharmacists made antibiotic recommendations as listed in the PCT algorithm below, which was adopted from previous studies that included critically ill patients. When making these recommendations, pharmacists had a collaborative discussion with the attending physician and accounted for patients' overall clinical status and objective data (e.g., microbiology results, WBC, bands, fevers, imaging). The choice of antibiotics and final decision with respect to continuing or discontinuing antibiotics was at the discretion of the attending physician. - If PCT is <0.1µg/L or reduces by >90%, cessation of antibiotics is *strongly encouraged* (but consider continuing antibiotics if patient is clinically unstable) - If PCT is 0.1-0.24µg/L or reduces by >80%, cessation of antibiotics is *encouraged (but consider continuing antibiotics if patient is clinically unstable)* - If PCT >= 0.25-0.5µg/L, cessation of antibiotics is *discouraged* - If PCT is >0.5µg/L, cessation of antibiotics is *strongly discouraged.* - If PCT is >0.25µg/L and rising, or not decreasing by at least 10% per day, this is a poor prognostic indicator; consider expanding antibiotic coverage or other diagnoses.
Comparator	The historical cohort did not undergo any intervention (usual care). Utilisation of PCT was low in the institution prior to introduction of the algorithm. In addition, patients in the historical cohort were excluded if they had 2 or more consecutive PCT levels ordered within 24 to 48 hours following antibiotic initiation to prevent inclusion of patients who may have had influence of PCT algorithm in their infection management
Outcome measures	Total antibiotic use - duration Mortality Length of hospital stay

	Length of ICU stay Re-initiation of antibiotic therapy for the initial infection within 72 hours of antibiotic discontinuation Incidence of C difficile
Number of participants	N = 74 (n= 37 in each group)
Duration of follow-up	28 days
Loss to follow-up	Not reported
Methods of analysis	Descriptive statistics (median and interquartile range) were used to describe variables in each group. Mann-Whitney U test was used to compare continuous variables and Pearson χ2 test or Fisher exact test was used to compare categorical variables.
Additional comments	Included patients with CAP, HAP and VAP, but incidence of VAP was low (5.4% in PCT group and 2.7% in control group).

CAP: community acquired pneumonia; HAP: hospital acquired pneumonia; ICU: intensive care unit; PCT: procalcitonin; N/A: not applicable; VAP: ventilator associated pneumonia

Characteristics

Arm-level characteristics

Characteristic	Pharmacist-led PCT group (N = 37)	Control group (N = 37)
% Female No of events	n = 18 ; % = 48.6	n = 15 ; % = 40.5
Age (SD) Median (IQR)	66 (52 to 76)	65 (54 to 79)
Coronary artery disease No of events	n = 14 ; % = 37.8	n = 8 ; % = 21.6
Congestive heart failure No of events	n = 13 ; % = 35.1	n = 9 ; % = 24.3
Cerebrovascular accident No of events	n = 4 ; % = 10.8	n = 5 ; % = 13.5
Chronic kidney disease No of events	n = 8 ; % = 21.6	n = 3 ; % = 8.1

COPD No of events	n = 11 ; % = 29.7	n = 13 ; % = 35.1
Diabetes mellitus No of events	n = 20 ; % = 54.1	n = 16 ; % = 43.2
CAP No of events	n = 31 ; % = 83.8	n = 29 ; % = 78.4
HAP No of events	n = 4 ; % = 10.8	n = 7 ; % = 18.9
VAP No of events	n = 2 ; % = 5.4	n = 1 ; % = 2.7
Mechanical ventilation No of events	n = 15 ; % = 40.5	n = 12 ; % = 32.4
Procalcitonin at baseline Median (IQR)	0.34 (0.2 to 0.7)	NR (NR to NR)

CAP: community acquired pneumonia; COPD: chronic obstructive pulmonary disease; HAP: hospital acquired pneumonia; IQR: interquartile range; NR: not reported; PCT: procalcitonin; VAP: ventilator associated pneumonia

Critical appraisal - CASP checklist for case-control studies

Overall risk of bias	Moderate: no baseline PCT measurement for control group at baseline so not possible to establish whether groups were comparable pre-intervention
Overall directness	Directly applicable (but ICU patients only)

Townsend, 2018

Bibliographic Reference	Townsend, Jennifer; Adams, Victoria; Galiatsatos, Panagis; Pearse, David; Pantle, Hardin; Masterson, Mary; Kisuule, Flora; Jacob, Elsen; Kiruthi, Catherine; Ortiz, Paul; Agbanlog, Albert; Jurao, Robert; Stern, Sam; Nayak, Seema; Melgar, Michael; Sama, Jacob; Irwin, Jillian; Mazidi, Cyrus; Psoter, Kevin; McKenzie, Robin; Procalcitonin-Guided Antibiotic Therapy Reduces Antibiotic Use for Lower Respiratory Tract Infections in a United States Medical Center: Results of a Clinical Trial.; Open forum infectious diseases; 2018; vol. 5 (no. 12); ofy327

Study details

Secondary publication of another included study- see primary study for details	N/A Note that this study was of all patients admitted with a diagnosis of LRTI but subgroup analyses are presented for patients with pneumonia. The data extracted here for the current review is from the sub-sample with CAP only.
Other publications associated with this study included in review	N/A
Trial registration number and/or trial name	ClinicalTrials.gov database number NCT0310910
Study type	Case-control study
Study location	United States
Study setting	Hospital
Study dates	Prospective intervention cohort: 17th April 2017 to 29th November 2017 Retrospective pre-intervention control cohort: 1st November 2016 to 16th April 2017
Sources of funding	This work was funded by B·R·A·H·M·S GmbH (ThermoFisher, Hennigsdorf, Germany), Grant Number 125346.
Inclusion criteria	Adult patients (>18 years) admitted to the hospital via the ED and receiving antibiotics for suspected LRTI for <48 hours at time of screening Inclusion criteria for LRTI were 1 symptom (cough, dyspnea, tachypnea, pleuritic pain) AND 1 sign compatible with acute LRTI (at least 1 finding during auscultation (crackles, egophony), or 1 sign of infection (core body temperature >38.^{0}C, shivering, or leukocyte count >10,000/μL or <4,000/μL) of less than 28 days duration
Exclusion criteria	Patients with cystic fibrosis Severely immunocompromised patients Patients unable to give informed consent due to language restriction or severe dementia

	Patients with active intravenous drug use Pregnant patients Patients diagnosed with a concomitant bacterial infection in addition to pneumonia at the time of antibiotic initiation
Intervention(s)	Pre-antibiotic PCT level was measured on blood left over from initial testing in the ED. Subsequent PCT levels were timed for 48 hours after baseline for patients admitted to the floor, or 24 hours after baseline for patients admitted to intensive care units (ICUs). PCT was repeated every 48 hours for non-ICU patients, and daily for ICU patients. PCT results were reviewed by an infectious disease (ID) pharmacist and an ID physician. The PCT levels were used only to guide antibiotic discontinuation decisions, and were based on previously published PCT algorithms. - If procalcitonin level < 0.1ug/L, bacterial infection highly unlikely, NO antibiotics! - If procalcitonin level 0.1-0.25ug/L, bacterial infection unlikely, no antibiotics. - If procalcitonin level 0.25-0.5ug/L, bacterial infection likely, antibiotics yes. - If procalcitonin level >0.5ug/L, bacterial infection / sepsis highly likely, antibiotics YES! - If procalcitonin level decreases by 80-90% from the peak value, or drops below <0.25ug/L (non-ICU) or <0.5ug/L (ICU), consider stopping antibiotics. Overruling of the PCT algorithm was allowed for prespecified criteria, including respiratory or hemodynamic instability, life-threatening comorbidity, ICU admission, and severe illness.
Comparator	Control patients were treated according to physician preference. Local treatment guidelines for pneumonia recommended antibiotic durations of 3–5 days for patients without immunocompromise or structural lung disease, 7 days with moderate immunocompromise or structural lung disease, and 10–14 days in patients with immunocompromise or poor initial response.
Outcome measures	Total antibiotic use - duration Length of hospital stay Overall adverse events by 30 days (composite of new antibiotic prescription for LRTI, transfer to an ICU, death, antibiotic side effects, disease-specific complications (i.e., persistence or development of new pneumonia, lung abscess, empyema, or

	acute respiratory distress syndrome), and Clostridium difficile infection.
Number of participants	Overall study sample N = 374 (procalcitonin group n=174; control group n=200) Pneumonia only sub-sample N = 255 (procalcitonin group n=130; control group n=125)
Duration of follow-up	30 days
Loss to follow-up	None reported
Methods of analysis	Demographic, clinical, and admitting data and outcomes were compared between the intervention and control groups using Student t tests and Wilcoxon rank-sum test for continuous variables and χ2 or Fisher exact tests for categorical variables. The proportion of patients experiencing an adverse event, as well as hospital readmission within 30 days, were compared, and the risk difference and 95% CI between the 2 groups were estimated.
Additional comments	The control period occurred during different parts of the calendar year, which may correspond to variations in antibiotic durations due to unmeasured factors such as the acquired experience among trainees and probability of admission based on fluctuating hospital volumes and seasonal variation in rates of respiratory illness. The authors argue that modifying antibiotic prescribing habits requires significant trust, feedback, and 2-way communication between prescribers and stewardship teams. They suggest it requires more than education and result alerting - more directive interventions are required. In this study, they established trust with prescribers via strong stakeholder buy-in. The study team included the medical directors of the ICU and hospitalist services, numerous front-line providers, clinical pharmacy staff, and the antimicrobial stewardship team. When PCT results were reported, the algorithm was displayed and the recommendation highlighted.

CAP: community acquired pneumonia; ED: emergency department; EMR: electronic medical record; ICU: intensive care unit; LRTI: lower respiratory tract infection; N/A: not applicable; PCT: procalcitonin

Characteristics

Arm-level characteristics

Characteristic	Procalcitonin group (N = 174)	Control group (N = 200)
% Female No of events	n = 103 ; % = 59	n = 105 ; % = 53

Age (SD) Mean (SD)	63.5 (14.3)	63.3 (14.9)
Smoking status No of events	n = 77 ; % = 44	n = 90 ; % = 45
Hypertension No of events	n = 119 ; % = 68	n = 131 ; % = 66
COPD No of events	n = 112 ; % = 64	n = 129 ; % = 65
Diabetes No of events	n = 55 ; % = 32	n = 51 ; % = 26
Congestive heart failure No of events	n = 56 ; % = 32	n = 72 ; % = 36
Asthma No of events	n = 25 ; % = 14	n = 19 ; % = 10
Chronic kidney disease No of events	n = 45 ; % = 26	n = 33 ; % = 17
Active malignancy No of events	n = 15 ; % = 9	n = 10 ; % = 5
Bronchiectasis No of events	n = 8 ; % = 5	n = 4 ; % = 2
Pneumonia No of events	n = 130 ; % = 75	n = 125 ; % = 63
AECOPD No of events	n = 36 ; % = 21	n = 64 ; % = 32
Other LRTI No of events	n = 8 ; % = 5	n = 11 ; % = 6
CURB-65 score 0 No of events	n = 25 ; % = 19	n = 18 ; % = 14
CURB-65 score 1	n = 46 ; % = 34	n = 47 ; % = 37

No of events		
CURB-65 score 2 No of events	n = 36 ; % = 27	n = 33 ; % = 26
CURB-65 score 3 No of events	n = 19 ; % = 14	n = 20 ; % = 16
CURB-65 score 4 No of events	n = 7 ; % = 5	n = 6 ; % = 5
CURB-65 score 5 No of events	n = 2 ; % = 2	n = 2 ; % = 2
Initial PCT value for pneumonia patients Median (IQR)	0.19 (0.09 to 0.61)	NR (NR to NR)

AECOPD: Acute exacerbations of chronic obstructive pulmonary disease; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; LRTI: lower respiratory tract infection; NR: not reported; PCT: procalcitonin; SD: standard deviation

Critical appraisal - CASP checklist for case-control studies

Overall risk of bias	Moderate: no baseline PCT measurement for control group at baseline so not possible to establish whether groups were comparable pre-intervention The control period occurred during different parts of the calendar year, which may correspond to variations in antibiotic durations due to unmeasured factors such seasonal variation in rates of respiratory illness.
Overall directness	Directly applicable (but ICU patients only)

ICU: intensive care unit

D.1.3 Prospective cohort study evidence

Andrijevic, 2014

Bibliographic Reference	Andrijevic, Ilija; Matijasevic, Jovan; Andrijevic, Ljiljana; Kovacevic, Tomi; Zaric, Bojan; Interleukin-6 and procalcitonin as biomarkers in mortality prediction of hospitalized patients with community acquired pneumonia.; Annals of thoracic medicine; 2014; vol. 9 (no. 3); 162-7

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: Serbia Study setting: University hospital Study dates: January 2010 to December 2012 Sources of funding: The study was supported by the grant of the Serbian Ministry of Science and Technology, grant number 175056.
Inclusion criteria	Patients over 18 years old with an established diagnosis of CAP according to IDSA (The Infectious Diseases Society of America) criteria, and chest X-ray (CXR) or thoracic CT scan suggestive for community acquired pneumonia.
Exclusion criteria	CXR or CT highly suggestive for lung cancer Hospital acquired or healthcare associated pneumonia Inability to comply with the study protocol
Number of participants and recruitment methods	148 adult inpatients were screened for the trial, of whom 101 met all inclusion criteria without any exclusions.
Length of follow-up	All surviving patients underwent 30 day follow-up.
Loss to follow up	No loss to follow-up
Outcome(s) of interest	Mortality within 30 days
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin
Covariates adjusted for in the multivariable regression modelling	N/A

CT: computed tomography; CXR: chest x-ray; N/A: not applicable

Population characteristics

Study-level characteristics

Characteristic	Study (N = 101)
% Female No of events	n = 25 ; % = 24.8
Age (SD) Mean (SD)	63.7 (11.8)
Current smoker No of events	n = 61 ; % = 60.4
Former smoker No of events	n = 10 ; % = 9.9
Non-smoker No of events	n = 30 ; % = 29.7
PSI score Range	39 to 227
PSI score Mean (SD)	113.5 (41.5)
Class 0 No of events	n = 12 ; % = 11.9
Class 1 No of events	n = 24 ; % = 23.8
Class 2 No of events	n = 26 ; % = 25.7
Class 3 No of events	n = 17 ; % = 16.8
Class 4 No of events	n = 15 ; % = 14.9
Class 5 No of events	n = 2 ; % = 2

Characteristic	Study (N = 101)
Class 6 No of events	n = 5 ; % = 5
Mortality at 30 days No of events	n = 25 ; % = 24.8

PSI: pneumonia severity index; SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Chalmers, 2008

Bibliographic Reference Chalmers, JD Singanayagam, A Hill, AT; C-reactive protein is an independent predictor of severity in community-acquired pneumonia; AMERICAN JOURNAL OF MEDICINE; 2008; vol. 121 (no. 3); 219 - 225

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: Scotland, UK Study setting: Large teaching hospital Study dates: February 2005 to February 2007 Sources of funding: Not reported
Inclusion criteria	All adult patients presenting to hospital with a diagnosis of CAP during the study period CAP defined as a history consistent with pneumonia (with 1 or more of the following: new-onset shortness of breath, cough, sputum production, haemoptysis, chest pain, new-onset confusion, or pyrexia) and new infiltrates on the chest radiograph. Patient records from the follow-up clinic were reviewed to ensure the discharge diagnosis was pneumonia and no exclusion criteria were present.
Exclusion criteria	Hospital-acquired pneumonia (HAP)

	Active thoracic or extrathoracic malignancy Conditions likely to cause diagnostic confusion or where chest radiograph changes are equivocal (e.g., pulmonary fibrosis, allergic bronchopulmonary aspergillosis) Chronic lung disease (chronic obstructive pulmonary disease, bronchiectasis, chronic asthma) Immunosuppression (iatrogenic or acquired) Solid organ transplant Haematological disorders including haematological malignancy Chronic liver disease or cirrhosis Other acute co-morbid illnesses leading to physiological or metabolic derangement such that pneumonia severity assessment would be inappropriate (e.g., acute pulmonary embolism) Patients for whom active treatment is not considered appropriate (e.g., palliative care)
Number of participants and recruitment methods	There were 936 patients considered for inclusion during the study period; 570 patients met the criteria and were included in the study. The main reasons for exclusion were chronic lung disease, active malignancy, HAP, and diagnosis of lung cancer or persistent shadowing on chest radiograph at follow-up.
Length of follow-up	30 days
Loss to follow up	No loss to follow-up reported
Outcome(s) of interest	30-day mortality Need for mechanical ventilation and/or inotropic support Development of complicated pneumonia (lung abscess, empyema, or complicated parapneumonic effusion)
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission C-reactive protein Day 4 C-reactive protein
Covariates adjusted for in the multivariable regression modelling	N/A

CAP: community acquired pneumonia; HAP: hospital acquired pneumonia; N/A: not applicable

Population characteristics

Study-level characteristics

Characteristic	Study (N = 570)
% Female No of events	n = 292 ; % = 51.2
Age (SD) Median (IQR)	62 (44 to 76)
Duration of hospital admission Median (IQR)	5 (2 to 11)
Current smoker No of events	n = 204 ; % = 36
Former smoker No of events	n = 145 ; % = 25
Non smoker No of events	n = 221 ; % = 39

IQR: interquartile range; SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Coelho, 2012

Bibliographic Reference	Coelho, Luis M; Salluh, Jorge I F; Soares, Marcio; Bozza, Fernando A; Verdeal, Juan Carlos R; Castro-Faria-Neto, Hugo C; Lapa e Silva, Jose Roberto; Bozza, Patricia T; Povoa, Pedro; Patterns of c-reactive protein RATIO response in severe community-acquired pneumonia: a cohort study.; Critical care (London, England); 2012; vol. 16 (no. 2); r53

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: Brazil and Portugal

	Study setting: ICU Study dates: November 2001 to December 2002 for Portugal study August 2003 to June 2007 for Brazil study Sources of funding: Not reported
Inclusion criteria	Patients admitted to ICU with severe CAP (diagnosed according to the American Thoracic Society criteria). CURB-65 was used to evaluate severity.
Exclusion criteria	Patients with severe immunosuppression (for example, from solid organ or bone marrow transplant, HIV infection, or immunosuppressive treatment) and tuberculosis were excluded
Number of participants and recruitment methods	191 patients with severe CAP requiring ICU admission were included.
Length of follow-up	Patients were followed until death or hospital discharge
Loss to follow up	Not reported
Outcome(s) of interest	Hospital mortality ICU mortality
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission C-reactive protein Day 5 C-reactive protein Day 7 C-reactive protein

CAP: community acquired pneumonia; HIV: human immunodeficiency virus; ICU: intensive care unit

Population characteristics

Study-level characteristics

Characteristic	Study (N = 191)
% Female No of events	n = 89 ; % = 46.6
Age (SD) Median (IQR)	70 (54 to 81)
ICU length of stay Median (IQR)	7 (4 to 15)

Characteristic	Study (N = 191)
Hospital length of stay Median (IQR)	13 (9 to 26)
Need for mechanical ventilation No of events	n = 111 ; % = 58.1
Septic shock at ICU admission No of events	n = 79 ; % = 41.3

ICU: intensive care unit: IQR: interquartile range; SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Cornelis 2012

Bibliographic Reference Cornelis P C de Jager 1, Peter C Wever, Eugenie F A Gemen, Ron Kusters, Arianne B van Gageldonk-Lafeber, Tom van der Poll RJFL; The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia; PLoS One; 2012; vol. 10 (no. 7)

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: The Netherlands Study setting: Emergency department (ED) of a large teaching hospital Study dates: December 2007 to January 2010 Sources of funding: The authors have no support or funding to report.
Inclusion criteria	Consecutive adult patients admitted to the ED with suspected CAP. Clinically suspected CAP was defined as the presence of symptoms of lower respiratory tract infection (new cough, sputum production, dyspnoea, hypo- or hyperthermia, altered breath sounds upon physical examination) in the presence of a new infiltrate on plain chest radiography.
Exclusion criteria	Patients transferred from another hospital or residence in a nursing home

Number of participants and recruitment methods	During the study period, 562 consecutive patients with the clinical suspicion of CAP were presented at the ED. Because of an alternative diagnosis, 99 patients were excluded. Of 463 remaining patients, 395 (85.3%) had a new infiltrate on chest radiography and were diagnosed with CAP.
Length of follow-up	30 days
Loss to follow up	No loss to follow-up reported
Outcome(s) of interest	Mortality within 30 days ICU admission Duration of hospitalisation
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission C-reactive protein Admission neutrophil to lymphocyte ratio

CAP: community acquired pneumonia; ED: emergency department; ICU: intensive care unit

Population characteristics

Study-level characteristics

Characteristic	Study (N = 395)
% Female No of events	n = 155 ; % = 39
Age (SD) Mean (SD)	63 (16)
Current smoker No of events	n = 151 ; % = 38

SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Curbelo, 2017

Bibliographic Reference	Curbelo, Jose; Luquero Bueno, Sergio; Galvan-Roman, Jose Maria; Ortega-Gomez, Mara; Rajas, Olga; Fernandez-Jimenez, Guillermo; Vega-Piris, Lorena; Rodriguez-Salvanes, Francisco; Arnalich, Belen; Diaz, Ana; Costa, Ramon; de la Fuente,

Hortensia; Lancho, Angel; Suarez, Carmen; Ancochea, Julio; Aspa, Javier; Inflammation biomarkers in blood as mortality predictors in community-acquired pneumonia admitted patients: Importance of comparison with neutrophil count percentage or neutrophil-lymphocyte ratio.; PloS one; 2017; vol. 12 (no. 3); e0173947

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: Spain Study setting: Hospital setting Study dates: October 2013 to July 2015 Sources of funding: This work was funded by the Instituto de Salud Carlos III (ES) - European Regional Development Fund - PI 12/01142 and PI 15/01231; and Spanish Respiratory Society - SEPAR 2013.
Inclusion criteria	Age over 18 years and being diagnosed with CAP in the emergency room and subsequently being hospitalised for this reason. The diagnosis of CAP was established by the presence of lower respiratory tract infection symptoms together with the appearance of new infiltrate in chest x-ray, and the absence of an alternative diagnosis.
Exclusion criteria	No exclusion criteria reported
Number of participants and recruitment methods	154 patients
Length of follow-up	90 days
Loss to follow up	No loss to follow-up reported
Outcome(s) of interest	Mortality within 30 days Mortality within 90 days
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission C-reactive protein 72–120-hour C-reactive protein Admission procalcitonin 72–120-hour procalcitonin Admission neutrophil to lymphocyte ratio 72–120-hour neutrophil to lymphocyte ratio

Additional comments	No study level characteristics reported in the paper.

CAP: community acquired pneumonia

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate: No baseline characteristics reported
Overall risk of bias and directness	Directness	Directly applicable

El Maghraby, 2020

Bibliographic Reference El Maghraby, Hanaa M; Ismail, Nagwan A; Mohammed, Heba A; Serum Procalcitonin as A Diagnostic and Prognostic Marker for Bacterial Community - Acquired Pneumonia.; The Egyptian journal of immunology; 2020; vol. 27 (no. 1); 37-44

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: Egypt Study setting: University hospital Study dates: June 2016 to August 2018 Sources of funding: Not reported
Inclusion criteria	Patients with acute illness diagnosed clinically and radiologically as CAP were included. Patients were diagnosed with CAP if their chest X rays showed new or increasing infiltration in the lung field in addition to one or more of lower respiratory tract infection presentation including (fever, cough, purulent sputum and focal chest signs).
Exclusion criteria	Age below 18 years History of hospitalisation within 28 days History of chronic renal disease Antimicrobial intake within 2 days Pregnant patients
Number of participants and	240 patients in total sample, but only 95 admitted to hospital and only 45 included in the sub-sample extracted for analysis

recruitment methods	
Length of follow-up	30 days
Loss to follow up	Not reported
Outcome(s) of interest	Mortality within 30 days
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin
Additional comments	Study characteristics are only reported for full sample; not sub-sample of hospitalised patients used in analyses.

CAP: community acquired pneumonia

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

El-dib, 2015

Bibliographic Reference El-dib, A.S.; El-Srougy, H.A.; Diagnostic and prognostic role of procalcitonin in CAP; Egyptian Journal of Chest Diseases and Tuberculosis; 2015; vol. 64 (no. 4); 871-875

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: Egypt Study setting: University hospital Study dates: December 2012 to December 2013 Sources of funding: Not reported
Inclusion criteria	Adult patients with clinical and radiological findings compatible with CAP (defined as an acute illness associated with at least one of the following symptoms as fever, new cough with or without sputum production, pleuritic chest pain, dyspnoea, or change in the colour of sputum in patients with chronic cough or signs as altered breath sound, rales, plus chest X ray showing an opacity compatible with acute pneumonia
Exclusion criteria	Patients with a prior hospitalization within 2 weeks of a current diagnosis of pneumonia

	Residence in a long-term care facility Antibiotic use in the prior 14 days
Number of participants and recruitment methods	50 patients
Length of follow-up	4 weeks or until death
Loss to follow up	Not reported
Outcome(s) of interest	CAP severity (severe CAP: requiring mechanical ventilation or vasopressor support for septic shock)
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin

CAP: community acquired pneumonia

Population characteristics

Study-level characteristics

Characteristic	Study (N = 50)
% Female No of events	n = 27 ; % = 54
Age (SD) Mean (SD)	46 (3.32)

SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Fernandes, 2015

Bibliographic Reference	Fernandes, Lalita; Arora, Akashdeep Singh; Mesquita, Anthony Menezes; Role of Semi-quantitative Serum Procalcitonin in Assessing Prognosis of Community Acquired Bacterial Pneumonia Compared to PORT PSI, CURB-65 and CRB-65.; Journal of clinical and diagnostic research : JCDR; 2015; vol. 9 (no. 7); oc01-4

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: Goa, India Study setting: Pulmonary medicine wards Study dates: January 2011 to July 2012 Sources of funding: Not reported
Inclusion criteria	Patients ≥15 years with radiographically confirmed pneumonia (new or progressive infiltrates on CXR or CT scan consistent with bacterial pneumonia), acute illness (≤ 7 days duration) with at least three of the following clinical signs or symptoms consistent with a lower respiratory tract infection – new or increased cough, purulent sputum or change in sputum character, auscultatory findings consistent with pneumonia (e.g., rales, egophony, findings of consolidation), dyspnoea, tachypnoea or hypoxemia, fever greater than 38 °C oral or hypothermia (<35 °C), white blood cell count greater than 10,000 cells/mm3 or less than 4,500 cells/mm3, greater than 15% immature neutrophils (bands) irrespective of WBC count.
Exclusion criteria	Patients with HIV seropositivity, on immunosuppressive drug therapy, pulmonary tuberculosis, pulmonary infarction, congestive cardiac failure, healthcare associated pneumonia, or aspiration pneumonia Patients with prior antibiotic therapy for the current pneumonia episode
Number of participants and recruitment methods	55 patients
Length of follow-up	30 days
Loss to follow up	Not reported
Outcome(s) of interest	Mortality within 30 days
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin

CT: computed tomography; CXR: chest x-ray; HIV: human immunodeficiency virus; WBC: white blood cells

Population characteristics

Study-level characteristics

Characteristic	Study (N = 55)
% Female No of events	n = 17 ; % = 30.9
Male Mean (SD)	44.2 (16.1)
Female Mean (SD)	46.4 (17.3)

SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Guo, 2018

Bibliographic Reference	Guo, Shuren; Mao, Xiaohuan; Liang, Ming; The moderate predictive value of serial serum CRP and PCT levels for the prognosis of hospitalized community-acquired pneumonia.; Respiratory research; 2018; vol. 19 (no. 1); 193

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: China Study setting: Hospital settings Study dates: January 2017 to December 2017 Sources of funding: This research received no specific grant from any funding agency in the public, commercial, or not for-profit sectors.
Inclusion criteria	Hospitalised patients with a radiologically confirmed diagnosis of pneumonia. Diagnosis of CAP required
Exclusion criteria	No exclusion criteria reported
Number of participants and recruitment methods	250 patients
Length of follow-up	30 days

Loss to follow up	Not reported
Outcome(s) of interest	Mortality within 30 days
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin Day 3 procalcitonin Day 5 procalcitonin Admission C-reactive protein Day 3 C-reactive protein Day 5 C-reactive protein

CAP: community acquired pneumonia

Population characteristics

Study-level characteristics

Characteristic	Study (N = 350)
% Female No of events	n = 146 ; % = 41.7
Age (SD) Mean (SD)	58.53 (19.1)
Class 0-2 No of events	n = 289 ; % = 82.5
Class 3-5 No of events	n = 61 ; % = 17.5

SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Huang, 2008

Bibliographic Reference	Huang DT; Weissfeld LA; Kellum JA; Yealy DM; Kong L; Martino M; Angus DC; ; Risk prediction with procalcitonin and clinical rules

in community-acquired pneumonia.; Annals of emergency medicine; 2008; vol. 52 (no. 1)

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: United States Study setting: Emergency departments Study dates: November 2001 to November 2003 Sources of funding: NIGMS R01 GM061992
Inclusion criteria	Patients 18 years and older with a clinical and radiological diagnosis of pneumonia.
Exclusion criteria	Patients transferred from another hospital, discharged from hospital within the prior 10 days, with an episode of pneumonia within the past 30 days, on chronic mechanical ventilation, with cystic fibrosis, with active pulmonary tuberculosis, with a known positive HIV antibody titre, having alcoholism with evidence of end-organ damage, admitted for palliative care, incarcerated, and pregnant women.
Number of participants and recruitment methods	1651 patients
Length of follow-up	30 days
Loss to follow up	Not reported
Outcome(s) of interest	Mortality within 30 days
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin

HIV: human immunodeficiency virus

Population characteristics

Study-level characteristics

Characteristic	Study (N = 1651)
% Female No of events	n = 791 ; % = 47.9
Age (SD) Mean (SD)	65 (18.5)

Characteristic	Study (N = 1651)
Prior antibiotics No of events	n = 271 ; % = 16
PSI class I, II No of events	n = 541 ; % = 39
PSI class III No of events	n = 297 ; % = 21
PSI class IV No of events	n = 419 ; % = 30
PSI class V No of events	n = 127 ; % = 9

PSI: pneumonia severity index; SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Hur, 2020

Bibliographic Reference	Hur, I.; Ozkan, S.; Halici, A.; Abatay, K.; Usul, E.; Cetin, E.; Aydin, F.N.; Role of plasma presepsin, procalcitonin and c-reactive protein levels in determining the severity and mortality of community-acquired pneumonia in the emergency department; Signa Vitae; 2020; vol. 16 (no. 2); 61-68

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: Turkey Study setting: Emergency departments Study dates: 20th March 2018 to 20th May 2018 Sources of funding: The study received financial support from the scientific research projects support program of the hospital (No. 69/1 dated April 24, 2018)

Inclusion criteria	Patients diagnosed with pneumonia during the study period. Pneumonia defined as newly emerging pulmonary infiltration indicated by chest radiography and at least two symptoms or a pyrexia complaint
Exclusion criteria	Patients hospitalised in the last 2 weeks Pregnant women Patients who received immunosuppression treatment Patients who had received antibiotic therapy Patients with pulmonary phthisis, and patients with diagnoses that might be confused with pneumonia such as pulmonary thromboembolism and decompensated heart failure. Patients whose comorbidities included COPD
Number of participants and recruitment methods	123 patients
Length of follow-up	30 days
Loss to follow up	Not reported
Outcome(s) of interest	Mortality within 30 days
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin Admission C-reactive protein
Covariates adjusted for in the multivariable regression modelling	N/A

COPD: chronic obstructive pulmonary disease; N/A: not applicable

Population characteristics

Study-level characteristics

Characteristic	Study (N = 123)
% Female No of events	n = 53 ; % = 43
Age (SD) Range	28 to 92

Characteristic	Study (N = 123)
Age (SD) Mean (SD)	71.54 (13.36)

SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Kumar, 2018

Bibliographic Reference	Kumar, S.; Jan, R.; Rasool, R.; Fomda, B.; Koul, P.; Shah, S.; Hafiz, U.; Qadri, S.; Masoodi, S.; Muzamil, M.; Utility of procalcitonin in predicting mortality among cases of hospital-acquired pneumonia: A North Indian study; Egyptian Journal of Chest Diseases and Tuberculosis; 2018; vol. 67 (no. 2); 126-135

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: India Study setting: Unclear, but patients were described as critically ill, so assumed inpatient hospital settings Study dates: September 2013 to September 2015 Sources of funding: Financial support and sponsorship: Nil
Inclusion criteria	All cases of HAP (including HCAP) seen during the eligible study period. Diagnosis based on ATS/IDSA guidelines
Exclusion criteria	Paediatric and immunocompromised patients were excluded
Number of participants and recruitment methods	60 patients
Length of follow-up	Unclear
Loss to follow up	Not reported
Outcome(s) of interest	In-hospital mortality

Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin
Covariates adjusted for in the multivariable regression modelling	N/A

ATS American Thoracic Society: HAP: hospital acquired pneumonia; HCAP: health care-associated pneumonia; IDSA: Infectious Diseases Society of America; N/A: not applicable

Population characteristics

Study-level characteristics

Characteristic	Study (N = 60)
% Female No of events	n = 24 ; % = 40
Age (SD) Range	17 to 90
Age (SD) Mean (SD)	57.1 (17.8)
Current smoker No of events	n = 33 ; % = 55
PSI score Mean (SD)	124.52 (50.49)

PSI: pneumonia severity index; SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Lacoma, 2012

Bibliographic Reference	Lacoma A; Rodríguez N; Prat C; Ruiz-Manzano J; Andreo F; Ramírez A; Bas A; Pérez M; Ausina V; Domínguez J; Usefulness of consecutive biomarkers measurement in the management of community-acquired pneumonia.; European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology; 2012; vol. 31 (no. 5)

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: Spain Study setting: Emergency departments Study dates: January 2006 to June 2006 Sources of funding: Not reported
Inclusion criteria	Adult patients admitted to the ED presenting with clinical signs of LRTI and a new infiltrate on chest radiograph.
Exclusion criteria	Nosocomial or healthcare-associated pneumonia Presence of tuberculosis or infection caused by fungi or other opportunistic microorganisms
Number of participants and recruitment methods	Samples from 92 patients were collected during the eligible study period, and 75 of these were considered, after retrospective analysis by expert clinicians, to have presented with CAP.
Length of follow-up	Unclear
Loss to follow up	Not reported
Outcome(s) of interest	Mortality ICU admission
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin
Covariates adjusted for in the multivariable regression modelling	N/A

CAP: community acquired pneumonia; ED: emergency department; ICU: intensive care unit; LRTI: lower respiratory tract infection; N/A: not applicable

Population characteristics

Study-level characteristics

Characteristic	Study (N = 75)
% Female No of events	n = 21 ; % = 28

Characteristic	Study (N = 75)
Age (SD) Mean (SD)	67 (17.9)
Current smoker No of events	n = 18 ; % = 24
Ex-smoker No of events	n = 30 ; % = 40
Non smoker No of events	n = 27 ; % = 36
PSI class I No of events	n = 5 ; % = 6.7
PSI class II No of events	n = 11 ; % = 14.7
PSI class III No of events	n = 15 ; % = 20
PSI class IV No of events	n = 34 ; % = 45.3
PSI class V No of events	n = 10 ; % = 13.3

PSI: pneumonia severity index; SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Naderi, 2015

Bibliographic Reference	Naderi, HamidReza; Sheybani, Fereshte; Sarvghad, MohammadReza; Nooghabi, Mehdi Jabbari; Can Procalcitonin Add to the Prognostic Power of the Severity Scoring System in Adults with Pneumonia?.; Tanaffos; 2015; vol. 14 (no. 2); 95-106

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: Iran Study setting: Hospital setting Study dates: Not reported Sources of funding: Not reported
Inclusion criteria	Patients requiring hospital admission with a diagnosis of CAP. The diagnostic criteria for CAP included a new infiltrate on chest radiograph in a patient with either fever or clinical signs and symptoms of lower respiratory tract infection (cough, sputum production, dyspnea, pleuritic chest pain, crackles on auscultation), or both.
Exclusion criteria	None reported
Number of participants and recruitment methods	120 patients
Length of follow-up	Unclear
Loss to follow up	Not reported
Outcome(s) of interest	Intensive vasopressor and respiratory support requirement In-hospital mortality
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin
Covariates adjusted for in the multivariable regression modelling	N/A

CAP: community acquired pneumonia; N/A: not applicable

Population characteristics

Study-level characteristics

Characteristic	Study (N = 120)
% Female No of events	n = 17
Age (SD) Mean (SD)	50.4 (22.6)

SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Park, 2012

Bibliographic Reference	Park JH; Wee JH; Choi SP; Oh SH; The value of procalcitonin level in community-acquired pneumonia in the ED.; The American journal of emergency medicine; 2012; vol. 30 (no. 7)

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: Korea Study setting: Emergency departments Study dates: May 2009 to August 2010 Sources of funding: None
Inclusion criteria	Patients over 18 years attending ED and diagnosed with CAP. CAP was defined as a new pulmonary infiltrate diagnosed by chest radiograph together with at least 1 respiratory symptom (fever, cough, sputum production, dyspnea, tachypnea, and pleuritic pain).
Exclusion criteria	Patients hospitalised within 14 days before the onset of symptoms Patients discharged home from the ED Immunocompromised patients (with HIV infection or haematologic malignancies) Patients who were subsequently diagnosed with TB
Number of participants and recruitment methods	126 patients
Length of follow-up	30 days
Loss to follow up	Not reported
Outcome(s) of interest	Mortality within 30 days

Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin
Covariates adjusted for in the multivariable regression modelling	N/A

CAP: community acquired pneumonia; ED: emergency department; HIV: human immunodeficiency virus; N/A: not applicable; TB: tuberculosis

Population characteristics

Study-level characteristics

Characteristic	Study (N = 126)
% Female No of events	n = 61 ; % = 48
Age (SD) Mean (SD)	64 (NR)
PSI class I No of events	n = 26 ; % = 20.6
PSI class II No of events	n = 23 ; % = 18.2
PSI class III No of events	n = 22 ; % = 17.5
PSI class IV No of events	n = 32 ; % = 25.4
PSI class V No of events	n = 23 ; % = 18.2

NR: not reported; PSI: pneumonia severity index; SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Siljan, 2019

Bibliographic Reference	Siljan, William W; Holter, Jan C; Michelsen, Annika E; Nymo, Stale H; Lauritzen, Trine; Oppen, Kjersti; Husebye, Einar; Ueland, Thor; Mollnes, Tom E; Aukrust, Pal; Heggelund, Lars; Inflammatory biomarkers are associated with aetiology and predict outcomes in community-acquired pneumonia: results of a 5-year follow-up cohort study.; ERJ open research; 2019; vol. 5 (no. 1)

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: Norway Study setting: Acute care general hospital Study dates: January 2008 to January 2011 Sources of funding: This work was supported by Vestre Viken Hospital Trust, Norway.
Inclusion criteria	Patients aged 18 years and over admitted with suspected CAP. CAP was defined by 1) a new pulmonary infiltrate on chest radiography, 2) rectal temperature >38.0°C and 3) at least one of the following symptoms or signs: cough (productive or non-productive), dyspnoea, respiratory chest pain, crackles or reduced respiratory sounds.
Exclusion criteria	Patients who had been hospitalised within the past 2 weeks or if the chest radiograph uncovered non-infectious findings
Number of participants and recruitment methods	267 patients
Length of follow-up	6 weeks
Loss to follow up	Not reported
Outcome(s) of interest	Adverse outcome (admission to ICU or 30-day mortality)
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin
Covariates adjusted for in the multivariable regression modelling	N/A

CAP: community acquired pneumonia; ICU: intensive care unit; N/A: not applicable

Population characteristics

Study-level characteristics

Characteristic	Study (N = 267)
% Female No of events	n = 127 ; % = 47.6
Age (SD) Median (IQR)	66 (52 to 78)
Current smoker No of events	n = 65 ; % = 24.4

IQR: interquartile range; SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Surme, 2020

Bibliographic Reference Surme, S.; Balkan, I.I.; Bayramlar, O.F.; Ali, R.K.; Mete, B.; Can, G.; Tabak, F.; Saltoglu, N.; Independent prognostic indicators in the elderly with pneumonia: A singlecentre prospective observational study; Turk Geriatri Dergisi; 2020; vol. 23 (no. 3); 342-352

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: Turkey Study setting: Hospital setting Study dates: January 2017 to December 2017 Sources of funding: Authors declare no funding was used
Inclusion criteria	Patients aged 18 years and older with CAP or HAP requiring hospitalisation. The diagnosis of pneumonia was made on the basis of current diagnostic guidelines.
Exclusion criteria	Outpatients, patients with neutropenia, and patients with CAP or post-operative pneumonia were excluded.

Number of participants and recruitment methods	184 patients
Length of follow-up	30 days
Loss to follow up	Not reported
Outcome(s) of interest	Poor prognosis (septic shock, ICU admission, or death within 30 days)
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin Admission C-reactive protein
Covariates adjusted for in the multivariable regression modelling	N/A

CAP: community acquired pneumonia; HAP: hospital acquired pneumonia; ICU: intensive care unit; N/A: not applicable

Population characteristics

Study-level characteristics

Characteristic	Study (N = 184)
% Female No of events	n = 74 ; % = 40.2
Age (SD) Mean (SE)	69.27 (1.23)
CAP No of events	n = 145 ; % = 78.8
HAP No of events	n = 39 ; % = 21.2
Smoking history No of events	n = 94 ; % = 51.1

CAP: community acquired pneumonia; HAP: hospital acquired pneumonia; SD: standard deviation; SE: standard error

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low

Section	Question	Answer
Overall risk of bias and directness	Directness	Directly applicable

Travlos, 2022

Bibliographic Reference	Travlos, Apostolos; Bakakos, Agamemnon; Vlachos, Konstantinos F; Rovina, Nikoletta; Koulouris, Nikolaos; Bakakos, Petros; C-Reactive Protein as a Predictor of Survival and Length of Hospital Stay in Community-Acquired Pneumonia.; Journal of personalized medicine; 2022; vol. 12 (no. 10)

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: Greece Study setting: University hospital setting Study dates: January 2013 to September 2019 Sources of funding: "This research received no external funding
Inclusion criteria	Adults with CAP
Exclusion criteria	Patients with hospital-acquired pneumonia (HAP), immunocompromised patients (hematologic malignancies, HIV, neutropenia < 1000 cells/mL, and patients who had received chemotherapy or other immunosuppressive therapy over the past 2 months) were excluded from the study. Patients who died within the first 2 days of CAP diagnosis Patients who received antibiotic treatment at least 1 day prior to hospital admission
Number of participants and recruitment methods	173 patients
Length of follow-up	30 days
Loss to follow up	Not reported
Outcome(s) of interest	Mortality within 30 days
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission C-reactive protein

Covariates adjusted for in the multivariable regression modelling	N/A
Additional comments	Study level characteristics reported by survival vs non-survival groups only; no data reported for full sample

CAP: community acquired pneumonia; N/A: not applicable

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Wang, 2022

Bibliographic Reference	Wang, Fei; Yang, Shuo; Liu, Chong; Xu, Zhen; Jia, Ke-Ke; Zhou, Jian-Suo; Cui, Li-Yan; Matrix Metalloproteinase 3: a Novel Effective Biomarker for Predicting the Mortality and the Severity of Pneumonia.; Clinical laboratory; 2022; vol. 68 (no. 1)

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: China Study setting: University hospital setting Study dates: June 2019 to January 2020 Sources of funding: Supported by research grants from programs of the Natural Science Foundation of China (61771022, 81800604).
Inclusion criteria	Adult patients with pneumonia admitted to the department of respiratory and critical care medicine during the eligible study period.
Exclusion criteria	Patients with pneumonia in the previous 30 days, active tuberculosis, pulmonary tumours, non-infectious interstitial diseases, pulmonary oedema, pulmonary embolism, pulmonary eosinophilic infiltration, pulmonary vasculitis, antibiotic therapy prior to admission or pregnancy, chronic inflammatory disorders (rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, and inflammatory bowel disease), acute kidney injury, mesangial proliferative glomerulonephritis, IgA nephropathy, and active lupus nephritis.

Number of participants and recruitment methods	185 patients
Length of follow-up	90 days from hospital admission or death
Loss to follow up	No loss to follow-up
Outcome(s) of interest	CAP severity (septic shock or need for mechanical ventilation) Mortality within 90 days
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin Admission C-reactive protein Admission neutrophil to lymphocyte ratio
Covariates adjusted for in the multivariable regression modelling	N/A

CAP: community acquired pneumonia; IgA: immunoglobin A: N/A: not applicable

Population characteristics

Study-level characteristics

Characteristic	Study (N = 185)
% Female No of events	n = 69 ; % = 37.3
Age (SD) Median (IQR)	67 (43.5 to 80)

IQR: interquartile range; SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Wang, 2020

Bibliographic Reference	Wang, J Gao, YY Zhu, J Huang, YM Li, W; Serum procalcitonin levels in predicting the prognosis of severe pneumonia patients and its correlation with white blood cell count and C-reactive

protein levels; INTERNATIONAL JOURNAL OF CLINICAL AND EXPERIMENTAL MEDICINE; 2020; vol. 13 (no. 2); 809 - 815

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: China Study setting: Hospital Study dates: January 2015 to January 2019 Sources of funding: Not reported
Inclusion criteria	Patients aged between 18 and 65 years with general or severe pneumonia.
Exclusion criteria	Patients complicated with other infections or serious diseases Patients with liver, kidney, heart, brain or other organ dysfunction Patients with low compliance
Number of participants and recruitment methods	148 patients (74 severe pneumonia; 74 general pneumonia)
Length of follow-up	28 days
Loss to follow up	Not reported
Outcome(s) of interest	Pneumonia severity (septic shock or need for ventilation) Mortality within 30 days
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin Admission C-reactive protein
Covariates adjusted for in the multivariable regression modelling	N/A

N/A: not applicable

Population characteristics

Study-level characteristics

Characteristic	Study (N = 148)
% Female	n = 63 ; % = 42.6

Characteristic	Study (N = 148)
No of events	
Age (SD) Mean (SD)	59.25 (9.6)

SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Wang, 2019

Bibliographic Reference	Wang, Yanhui; Zhang, Shan; Li, Liang; Xie, Juan; The usefulness of serum procalcitonin, C-reactive protein, soluble triggering receptor expressed on myeloid cells 1 and Clinical Pulmonary Infection Score for evaluation of severity and prognosis of community-acquired pneumonia in elderly patients.; Archives of gerontology and geriatrics; 2019; vol. 80; 53-57

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: China Study setting: Hospital setting Study dates: January 2015 and June 2016 Sources of funding: This work was supported by Natural science research project of Minhang District, Shanghai (Grant number 2014MHZ064).
Inclusion criteria	Elderly patients aged over 65 hospitalised with CAP. CAP was confirmed in accordance with the diagnostic criteria in “Guidelines for the diagnosis and treatment of CAP” issued by the respiratory branch of Chinese Medical Association in 2006 as follows: the chest X-ray examination of patients showed patchy infiltrate shadows or an interstitial change, and the patients developed any of the following symptoms: 1) symptoms of the original respiratory diseases worsened or cough and sputum newly emerged, and purulent sputum presented with or without chest pain; 2) a fever; 3) signs of lung consolidation and (or) moist rales; 4) the white

	blood count (WBC)>10×109/L or<4×109/L, with or without a shift of nuclei to the left.
Exclusion criteria	Patients whose clinical symptoms improved significantly and lung lesions showed obvious absorption without antimicrobial therapy Constant presence of severe heart, brain, kidney, vascular diseases, or a tumour. Autoimmune diseases Concurrent infection at another site History of special treatments within the previous month, including radiation therapy, chemotherapy, surgery, biological therapy , or immunosuppressive therapy.
Number of participants and recruitment methods	214 patients
Length of follow-up	Until hospital discharge or death
Loss to follow up	Not reported
Outcome(s) of interest	Mortality
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin Admission C-reactive protein
Covariates adjusted for in the multivariable regression modelling	N/A

CAP: community acquired pneumonia; N/A: not applicable

Population characteristics

Study-level characteristics

Characteristic	Study (N = 214)
% Female No of events	n = 87 ; % = 40.6
Age (SD) Mean (SD)	79.43 (7.05)

SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Zhang, 2023

Bibliographic Reference	Zhang, C.; Zheng, F.; Wu, X.; Predictive value of C-reactive protein-to-albumin ratio for risk of 28-day mortality in patients with severe pneumonia; Journal of Laboratory Medicine; 2023; vol. 47 (no. 3); 115-120

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: China Study setting: Hospital setting Study dates: January 2020 to January 2022 Sources of funding: None declared
Inclusion criteria	Patients conforming to the diagnostic criteria for severe pneumonia formulated by the Respiratory Society of the Chinese Medical Association and having complete clinical data
Exclusion criteria	Patients complicated with malignancies, severe blood diseases, pulmonary tuberculosis, or asthma were excluded.
Number of participants and recruitment methods	152 patients
Length of follow-up	28 days
Loss to follow up	Not reported
Outcome(s) of interest	Mortality within 30 days
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin Admission C-reactive protein Admission neutrophil to lymphocyte ratio
Covariates adjusted for in the	N/A

multivariable regression modelling	

N/A: not applicable

Population characteristics

Study-level characteristics

Characteristic	Study (N = 152)
% Female No of events	n = 78 ; % = 51.3
Age (SD) Mean (SD)	68.69 (3.16)

SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Zhou, 2018

Bibliographic Reference	Zhou, Haijiang; Guo, Shubin; Lan, Tianfei; Ma, Shuai; Zhang, Fang; Zhao, Zhiling; Risk stratification and prediction value of procalcitonin and clinical severity scores for community-acquired pneumonia in ED.; The American journal of emergency medicine; 2018; vol. 36 (no. 12); 2155-2160

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: China Study setting: Large University hospital Study dates: January 2016 to October 2017 Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Inclusion criteria	Adult patients who fulfilled CAP criteria and were admitted to the hospital ED during the eligible study period

Exclusion criteria	Age < 18 years Patients with metastatic tumour, AIDs, uremia, late stage liver cirrhosis, active tuberculosis, refractory heart failure, previous transplantation, immunosuppressive therapy, and pregnancy. Patients from a hospice or patients with DNR request
Number of participants and recruitment methods	226 participants
Length of follow-up	28 days
Loss to follow up	Not reported
Outcome(s) of interest	CAP severity (septic shock or need for mechanical ventilation) Mortality within 30 days
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission procalcitonin
Covariates adjusted for in the multivariable regression modelling	N/A

CAP: community acquired pneumonia; DNR: no not resuscitate; ED: emergency department; N/R: not reported

Population characteristics

Study-level characteristics

Characteristic	Study (N = 226)
% Female No of events	n = 36 ; % = 15.9
Age (SD) Mean (SD)	65 (NR)

NR: not reported; SD: standard deviation

Critical appraisal - GDT Crit App - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

D.2 Babies, children and young people

D.2.1 RCT evidence

Baer, 2013

Bibliographic Reference	Baer, Gurli; Baumann, Philipp; Buettcher, Michael; Heininger, Ulrich; Berthet, Gerald; Schafer, Juliane; Bucher, Heiner C; Trachsel, Daniel; Schneider, Jacques; Gambon, Muriel; Reppucci, Diana; Bonhoeffer, Jessica M; Stahelin-Massik, Jody; Schuetz, Philipp; Mueller, Beat; Szinnai, Gabor; Schaad, Urs B; Bonhoeffer, Jan; Procalcitonin guidance to reduce antibiotic treatment of lower respiratory tract infection in children and adolescents (ProPAED): a randomized controlled trial.; PloS one; 2013; vol. 8 (no. 8); e68419

Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	N/A
Trial registration number and/or trial name	ISRCTN17057980 ProPAED study
Study type	Randomised controlled trial (RCT)
Study location	Switzerland
Study setting	Emergency departments of two paediatric hospitals
Study dates	January 2009 to February 2010
Sources of funding	The Division of Infectious Diseases and Vaccines, University Children's Hospital, Basel, Switzerland supported this work as an investigator-initiated trial. Procalcitonin test kits and platform were provided by B.R.A.H.M.S. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Inclusion criteria	All children and adolescents, aged 1 month to 18 years of age, presenting with LRTI to the ED of 2 paediatric hospitals during eligible study period. Acute LRTI was defined as the presence of fever (core body temperature 38 °C measured in hospital or at home) and at least one symptom (cough, sputum production, pleuritic pain, poor feeding) and at least one sign (tachypnoea, dyspnoea, wheezing, late inspiratory crackles, bronchial breathing, pleural rub) for less than 14 days. In the case of fever, poor feeding and tachypnoea without other signs, persistence of tachypnoea following effective antipyretic treatment was required. Community acquired pneumonia (CAP) was defined as acute febrile LRTI with a new or increasing alveolar infiltrate on chest radiograph as assessed by the attending paediatrician.
Exclusion criteria	Patients were excluded if they or their care-takers were unwilling to participate or were unable to give written informed consent due to language problems
Intervention(s)	**Procalcitonin-guided antibiotic treatment.** Initiation, continuation or termination of antibiotic treatment was strictly guided by PCT cut-off levels used in previous trials in adults with LRTI . The algorithm provides PCT based decision categories for the likelihood of requiring antibiotic treatment for bacterial LRTI: ‘‘definitely’’ (>0.5 µg/L) ‘‘probably’’ (0.26–0.5 µg/L) ‘‘probably not’’ (0.1–0.25 µg/L) ‘‘definitely not’’ (<0.1 µg/L) For all patients, discontinuation of antibiotics was encouraged upon clinical stabilization and when PCT values fell below 0.25µg/L; or for patients with initial PCT values >10 µg/L, when levels decreased below 90% of the initial value. Continuation of treatment on day 5 was determined according to the following algorithm: >1 µg/L: 7 days, 0.51–1 µg/L: 5 days, 0.26–0.5 µg/L: 3 days, and ≤0.25 mg/L: no antibiotic. The PCT algorithm could be overruled for patients with life threatening infections, defined as severe co-morbidity, emerging ICU need during initial follow-up, or hemodynamic or respiratory instability.
Comparator	**Clinically guided standard care.**

	Antibiotic treatment was initiated based on physician assessment and clinical guidelines for a duration of 7–10 days for uncomplicated CAP and 14 or more days for complicated CAP, e.g., parapneumonic effusions, empyema, abscess
Outcome measures	Duration of antibiotic treatment Antibiotic prescription within 14 days of randomisation Antibiotic side effects (rash, vomiting, diarrhoea) Hospitalisation Duration of hospitalisation Occurrence of complications (e.g., parapneumonic effusions, empyema, lung abscess, necrotising pneumonitis, ARDS) or serious adverse events (e.g., hospital readmission, admission to ICU, unexpected life-threatening condition, death), or disease specific failure (e.g., recurrent infection in need of antibiotics, or development of any co-morbid condition requiring antibiotics irrespective of primary LRTI diagnosis, worsening of condition, new onset of respiratory distress)
Number of participants	N = 337 in full LRTI sample; n = 215 in CAP only sample
Duration of follow-up	14 days
Loss to follow-up	Follow-up was complete for 329 (98%) patients
Methods of analysis	An intention-to-treat analysis was used. A two-sided chi squared test was used to compare the primary endpoints (antibiotic prescribing within 14 days of randomization) between PCT and control groups. The rate difference and the odds ratio were estimated by logistic regression.
Additional comments	Baseline characteristics are provided for the full LRTI sample only (n = 337); not for the CAP subgroup (n = 215).

ARDS: acute respiratory distress syndrome; CAP: community acquired pneumonia; ED: emergency department; LRTI: lower respiratory tract infection; N/A: not applicable; PCT: procalcitonin

Study Characteristics

Arm-level characteristics

Characteristic	PCT group (N = 168)	Control group (N = 169)
% Female No of events	n = 70 ; % = 42	n = 71 ; % = 42
Age (SD)	2.7 (1.1 to 5.2)	2.9 (1.2 to 5.7)

Characteristic	PCT group (N = 168)	Control group (N = 169)
Median (IQR)		
0-2x No of events	n = 115 ; % = 74	n = 112 ; % = 74
>=3x No of events	n = 40 ; % = 26	n = 39 ; % = 26
0-2x No of events	n = 28 ; % = 18	n = 27 ; % = 17
>=3x No of events	n = 129 ; % = 82	n = 128 ; % = 83
Antibiotic pre-treatment No of events	n = 25 ; % = 15	n = 17 ; % = 10

IQR: interquartile range; PCT: procalcitonin; SD: standard deviation

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Some concerns about measurement of the outcome; relied on self-assessments and patient/caregiver diary entries.)*
Overall bias and Directness	Overall Directness	Directly applicable

Esposito, 2011

Bibliographic Reference	Esposito, Susanna; Tagliabue, Claudia; Picciolli, Irene; Semino, Margherita; Sabatini, Caterina; Consolo, Silvia; Bosis, Samantha; Pinzani, Raffaella; Principi, Nicola; Procalcitonin measurements for guiding antibiotic treatment in pediatric pneumonia.; Respiratory medicine; 2011; vol. 105 (no. 12); 1939-45

Study details

Secondary publication of another included study- see	N/A

primary study for details	
Other publications associated with this study included in review	N/A
Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Milan, Italy
Study setting	Paediatric hospital
Study dates	October 2008 to September 2010
Sources of funding	This study was supported by the Italian Ministry of Health (Bando Giovani Ricercatori 2007).
Inclusion criteria	Children aged > 1 month and < 14 years old with a diagnosis of CAP made on the basis of clinical signs and symptoms (i.e. a history of fever or cough, tachypnoea, dyspnoea or respiratory distress, and breathing with grunting or wheezing sounds with rales) and confirmed by chest radiography (i.e. the presence of pulmonary infiltration or segmental or lobar consolidation)
Exclusion criteria	Patients with pneumonia complications (i.e. plural effusion, lung necrosis, pneumatocele). Children who had received antibiotics in the 10 days preceding admission. Children suffering from an underlying chronic disease (e.g., anatomic abnormalities of the respiratory tract, immunological deficits, progressing neurological conditions, psychomotor retardation, congenital heart disease, haemoglobinopathy), severe malnutrition or other concurrent infections.
Intervention(s)	Antibiotics were not administered to the children with admission PCT levels of <0.25 ng/mL, but were immediately given in the case of higher values. The untreated children were given antibiotics only if their PCT levels increased to ≥0.25 ng/mL, and continued the therapy until the levels had returned to this value. The children who received antibiotics from the time of admission were treated until their PCT levels were <0.25 ng/mL, and resumed antibiotics only if their PCT levels subsequently increased to more than this value.

	The Italian Society of Paediatrics (SIP) guidelines for the management of paediatric CAP were used when choosing the antibiotic regimen. In the case of mild CAP, these guidelines recommend the use of oral amoxicillin for children aged <4 years and oral clarithromycin for those aged ≥4 years; in severe cases regardless of age, the recommended treatment is oral amoxicillin-clavulanate or intravenous (i.v.) cefotaxime plus oral or i.v. clarithomycin. All of the patients were clinically reassessed every day during hospitalisation. Untreated children showing no reduction in the clinical signs and symptoms of disease after three days could be treated with antibiotics regardless of their PCT levels. Moreover, in the case of severe clinical deterioration and regardless of their PCT levels, the children in both groups could be treated with antibiotics (if previously untreated) or their treatment could be modified on the basis of their paediatrician's judgment.
Comparator	The children in the control group were always treated in accordance with the SIP guidelines: antibiotic monotherapy chosen on the basis of age if mild; combined beta-lactam and macrolide therapy if severe. The duration of administration in the control group was that recommended by the SIP (i.e. 7-14 days depending on disease severity).
Outcome measures	Antibiotic side effects (rash, vomiting, diarrhoea) Duration of hospitalisation Recurrence of respiratory symptoms within 28 days New antibiotic prescription
Number of participants	310
Duration of follow-up	14 days and 28 days after admission
Loss to follow-up	No loss to follow-up
Methods of analysis	Pre-study power calculations (with 90% power) showed that 76 patients in each group were necessary to detect a 15% lower antibiotic use, considering that 100% of children hospitalized for CAP were treated with antibiotics and assuming a two-tailed test and a 5% level of significance. The discrete variables were expressed as absolute numbers (percentages), and the continuous variables as mean values plus standard deviation (SD), unless stated otherwise. The comparability of the treatment groups group was analysed using the Fisher’s exact test, the chi-square test, a two-sample t-test or the non-parametric Mann-Whitney U-test, as appropriate. A double-sided p value of <0.05 was considered significant.

CAP: community acquired pneumonia; N/A: not applicable; PCT: procalcitonin

Study Characteristics
Arm-level characteristics

Characteristic	PCT group (N = 155)	Control group (N = 155)
% Female No of events	n = 70 ; % = 45	n = 67 ; % = 43
Age (SD) Mean (SD)	4.31 (3.76)	4.67 (3.96)
Age < 4 years No of events	n = 76 ; % = 49	n = 74 ; % = 48
Age < 4 years No of events	n = 79 ; % = 51	n = 81 ; % = 52
Number of respiratory infections in previous 12 months Mean (SD)	2.97 (1.85)	2.63 (1.79)
Vaccinated with heptavalent pneumococcal conjugated vaccine No of events	n = 52 ; % = 33.5	n = 58 ; % = 37.4
Vaccinated with influenza vaccine No of events	n = 9 ; % = 5.8	n = 11 ; % = 7.1

PCT: procalcitonin; SD: standard deviation

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Trial not registered)*
Overall bias and Directness	Overall Directness	Directly applicable

D.2.2 Prospective cohort study evidence

Florin, 2020

Bibliographic Reference	Florin, Todd A; Ambroggio, Lilliam; Brokamp, Cole; Zhang, Yin; Rattan, Mantosh; Crotty, Eric; Belsky, Michael A; Krueger, Sara;

Epperson, Thomas N 4th; Kachelmeyer, Andrea; Ruddy, Richard; Shah, Samir S; Biomarkers and Disease Severity in Children With Community-Acquired Pneumonia.; Pediatrics; 2020; vol. 145 (no. 6)

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: USA Study setting: Emergency Departments of a children's hospital Study dates: July 2013 to December 2017 Sources of funding: National Institutes of Health National Institute of Allergy and Infectious Diseases, the Gerber Foundation, the National Institutes of Health National Center for Research Resources, and the Cincinnati Center for Clinical and Translational Science and Training.
Inclusion criteria	Children aged 3 months to 18 years with signs and symptoms of LRTI and focal findings on a CXR indicating suspected CAP. LRTI was defined as ≥1 of the following: new or different cough or sputum production, chest pain, dyspnoea, tachypnoea, or abnormal auscultatory findings. CXRs indicating CAP were defined as those showing focal opacities documented by the radiologist during the ED visit.
Exclusion criteria	Children hospitalised for ≤14 days before the index ED visit; those with a history of aspiration or aspiration pneumonia; and those with immunocompromising or chronic medical conditions that predispose to severe or recurrent pneumonia (e.g., immunodeficiency, chronic corticosteroid use, chronic lung disease, malignancy, sickle cell disease, congenital heart disease, patients dependent on tracheostomy, and neuromuscular disorders impacting respiration).
Number of participants and recruitment methods	Overall, 1142 children with LRTI were enrolled into the trial, of which 477 had a focal CXR opacity and had blood samples taken at admission.
Length of follow-up	7 to 15 days after discharge from ED or hospital
Loss to follow up	No loss to follow-up reported
Outcome(s) of interest	Development of complicated pneumonia ICU admission Development of severe sepsis or septic shock

	Need for positive-pressure ventilation Mortality
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission CRP Admission Procalcitonin
Covariates adjusted for in the multivariable regression modelling	N/A

CAP: community acquired pneumonia; CRP: C-reactive protein; CXR: chest x-ray; ED: emergency department; ICU: intensive care unit; LRTI: lower respiratory tract infection; N/A: not applicable

Population characteristics

Study-level characteristics

Characteristic	Study (N = 477)
% Female No of events	n = 226 ; % = 47.4
Age (SD) Mean (SD)	5.6 (4.6)
Pneumonia severity: Mild No of events	n = 121 ; % = 25.4
Pneumonia severity: Mild to moderate No of events	n = 126 ; % = 26.4
Pneumonia severity: Moderate to severe No of events	n = 179 ; % = 37.5
Pneumonia severity: Severe No of events	n = 51 ; % = 10.7

SD: standard deviation

Critical appraisal - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Golubeva, 2021

Bibliographic Reference	Golubeva, M.V.; Rakitina, E.N.; Minaev, S.V.; Kirgizov, I.V.; Obedin, A.N.; Akselrov, M.A.; Barova, N.K.; Bochnyuk, E.A.; Predictive role of bactericidal/permeability-increasing protein and C-reactive protein in a personalized approach to the treatment of children with acute pneumonia; Medical News of North Caucasus; 2021; vol. 16 (no. 2); 144-148

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: Russia Study setting: Hospital settings Study dates: Not reported Sources of funding: The study was carried out within the framework of the academic project «Development of research in the field of clinical medicine» of the Stavropol State Medical University Development Program.
Inclusion criteria	Age 2-18 years with an X-ray confirmed diagnosis of pneumonia; absence of severe concomitant pathology, absence of allergic reactions to administration of drugs.
Exclusion criteria	Previous hospitalisation that required the administration of antibiotic treatment within the previous 30 days; nosocomial pneumonia; concomitant somatic and infectious diseases; use of glucocorticoids; refusal of patients and their parents to participate in the study.
Number of participants and recruitment methods	165 children - 82 (49.7%) had acute pneumonia; 32 (19.4%) had a progression of illness or lack of response to treatment; and 51 (30.9%) had acute necrotising pneumonia.
Length of follow-up	14 days
Loss to follow up	Not reported
Outcome(s) of interest	Pneumonia severity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission CRP Day 3 CRP Day 14 CRP
Covariates adjusted for in the	N/A

multivariable regression modelling	
Additional comments	This study is poorly reported. Limited detail available on recruitment, including recruitment period, and sample characteristics. Limited methodological information regarding follow-up assessment and outcomes.

CRP: C-reactive protein; N/A: not applicable

Population characteristics

Study-level characteristics

Characteristic	Study (N = 165)
% Female No of events	n = 73 ; % = 44.8

Critical appraisal QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High *(Very limited methodological information provided; limited information on recruitment process, location or timeframe. Limited information on outcome assessment.)*
Overall risk of bias and directness	Directness	Directly applicable

Song, 2022

Bibliographic Reference	Song, Yunjing; Yang, Junmei; Sun, Hongqi; Mu, Xin; Serum levels of sirtuin 6 are associated with severe community acquired pneumonia in children: An observational study.; Cirugia y cirujanos; 2022; vol. 90 (no. 5); 632-637

Study Characteristics

Study design	Prospective cohort study
Study details	Study location: China Study setting: Hospital setting

	Study dates: January 2018 to December 2020 Sources of funding: The authors declare no funding
Inclusion criteria	Children diagnosed with CAP. The diagnosis criteria for CAP were: (1) patients with cough, expectoration, or aggravation of the original respiratory symptoms, purulent sputum, with or without chest pain; (2) fever; (3) signs of lung consolidation and/ or auscultation of wet rales; (4) WBC > 10 × 109/L or < 4.0 × 109/L, with or without left shift of neutrophils' nucleus; and (5) imaging examination showing patchy or patchy infiltration shadow or interstitial changes, with or without pleural effusion. Patients with any one of (1)~(4) and (5) were diagnosed as CAP.
Exclusion criteria	The following patients were excluded: (1) patients had taken antibiotics, antiviral drugs, or anti-inflammatory drugs within 3 months before the study; (2) patients with chronic inflammatory diseases such as asthma; and (3) patients with congenital diseases such as congenital heart disease and congenital hypothyroidism.
Number of participants and recruitment methods	150 patients: 75 with severe CAP and 75 with mild/moderate CAP
Length of follow-up	1 month
Loss to follow up	Not reported
Outcome(s) of interest	CAP severity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Admission CRP Admission PCT Admission NLR
Covariates adjusted for in the multivariable regression modelling	N/A
Additional comments	No information on eligible age range or included age range.

CAP: community acquired pneumonia; CRP: C-reactive protein; N/A: not applicable; NLR: neutrophil-to-lymphocyte ratio; PCT: procalcitonin; WBC: white blood cells

Population characteristics

Study-level characteristics

Characteristic	Study (N = 150)
% Female No of events	n = 61 ; % = 40.7
0-4 years No of events	n = 75 ; % = 50
5-14 years No of events	n = 75 ; % = 50

Critical appraisal - QUIPS checklist (prognostic)

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(No information on inclusion criteria for age - no eligible age range reported, only "children")*
Overall risk of bias and directness	Directness	Directly applicable

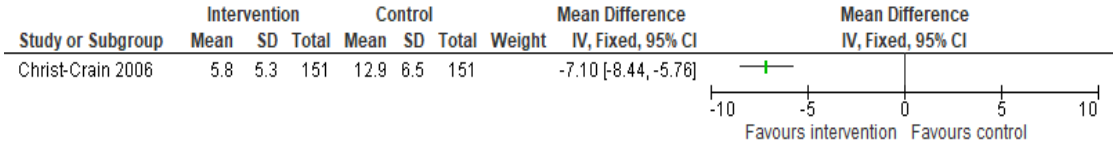
Appendix E – Forest plots

E.1 Adults

E.1.1 Procalcitonin-guided antibiotic treatment vs usual care in adults with pneumonia

Figure 1: Duration of antibiotic treatment (in days)

Lower scores favour PCT intervention group



CI: confidence interval; IV: inverse variance; PCT: procalcitonin; SD: standard deviation

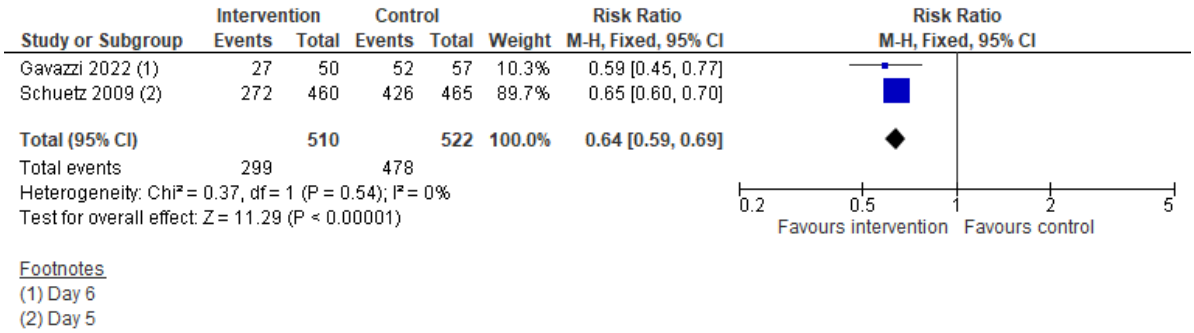
Figure 2: Antibiotics prescribed

Lower scores favour PCT intervention group

CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin

Figure 3: Antibiotic use on day 5 or day 6

Lower scores favour PCT intervention group



Footnotes
(1) Day 6
(2) Day 5

CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin

Figure 4: Antibiotic use on day 7 or day 8

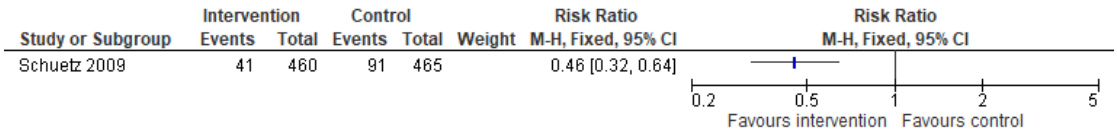
Lower scores favour PCT intervention group

Footnotes
(1) Day 8
(2) Day 7

CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin

Figure 5: Antibiotic use after day 13

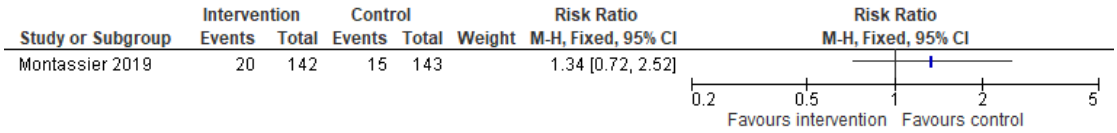
Lower scores favour PCT intervention group



CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin

Figure 6: New antibiotic prescription after hospitalisation (RCT only)

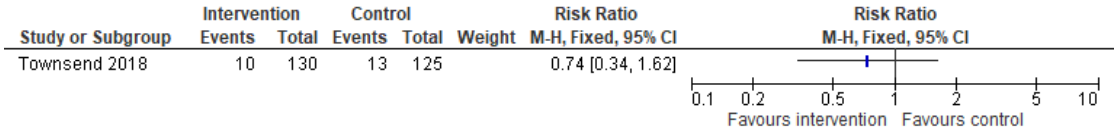
Lower scores favour PCT intervention group



CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin; RCT: randomised controlled trial

Figure 7: New antibiotic prescription after hospitalisation (non-RCT only)

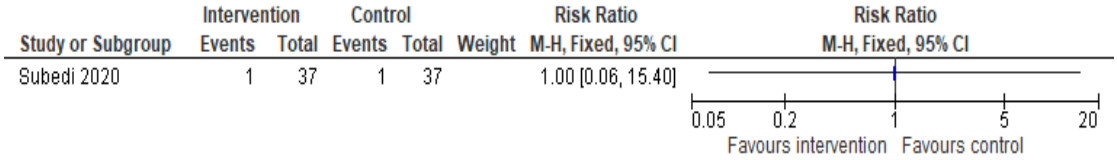
Lower scores favour PCT intervention group



CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin; RCT: randomised controlled trial

Figure 8: Re-initiation of antibiotics within 72 hours of discontinuation

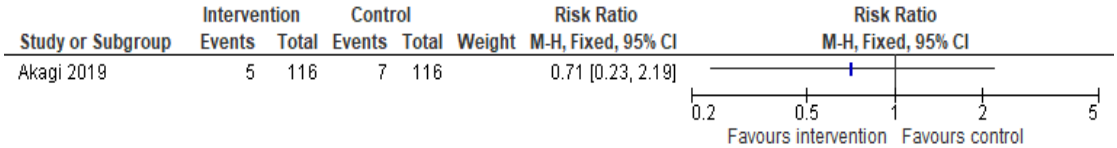
Lower scores favour PCT intervention group



CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin

Figure 9: Pneumonia recurrence after antibiotic discontinuation

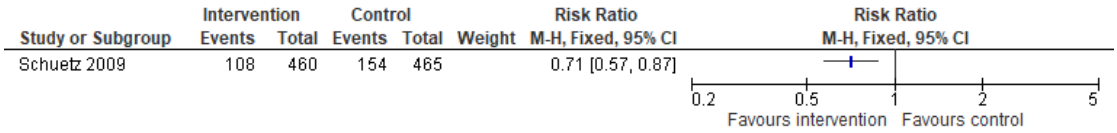
Lower scores favour PCT intervention group



CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin

Figure 10: Adverse events from antibiotic treatment (including nausea, diarrhoea and rash) (RCT only)

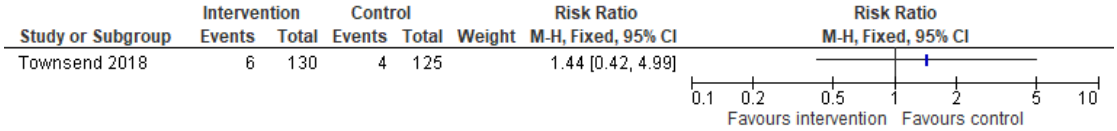
Lower scores favour PCT intervention group



CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin; RCT: randomised controlled trial

Figure 11: Adverse events from antibiotic treatment (including nausea, diarrhoea and rash) (non-RCT only)

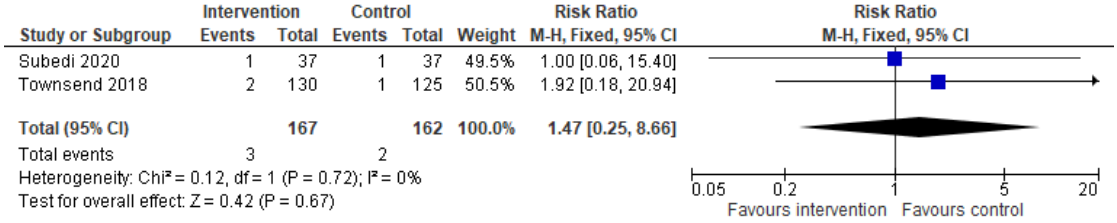
Lower scores favour PCT intervention group



CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin; RCT: randomised controlled trial

Figure 12: *C. diff.* infection

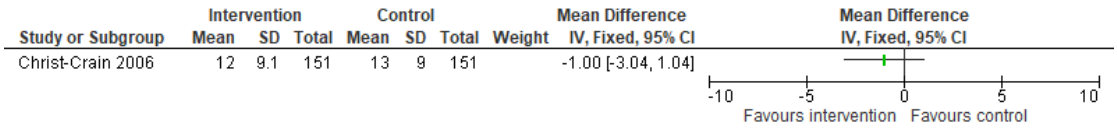
Lower scores favour PCT intervention group



CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin

Figure 13: Length of hospitalisation

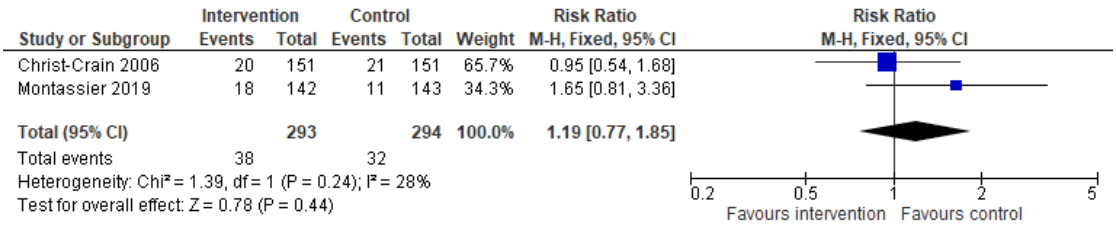
Lower scores favour PCT intervention group



CI: confidence interval; IV: inverse variance; PCT: procalcitonin; SD: standard deviation

Figure 14: Need for ICU admission (RCT only)

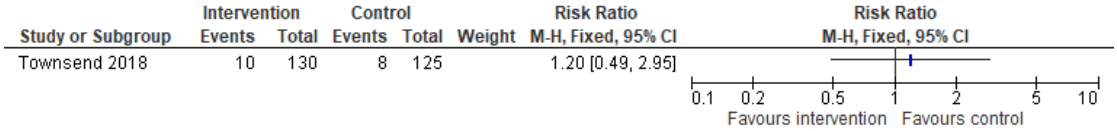
Lower scores favour PCT intervention group



CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin; RCT: randomised controlled trial

Figure 15: Need for ICU admission (non-RCT)

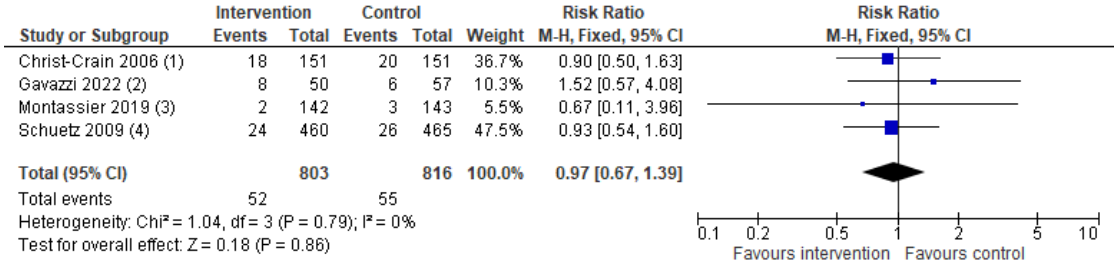
Lower scores favour PCT intervention group



CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin; RCT: randomised controlled trial

Figure 16: All-cause mortality (RCT only)

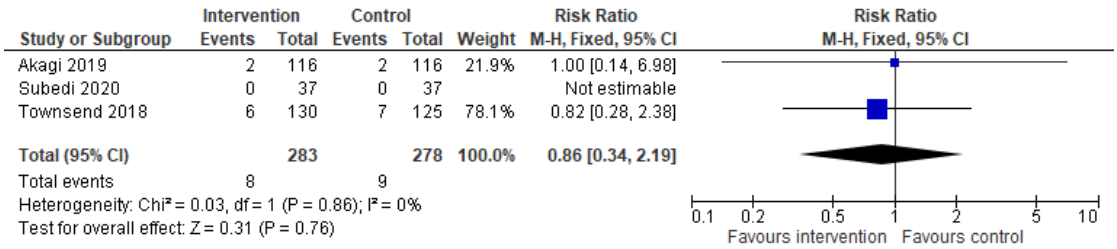
Lower scores favour PCT intervention group



CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin; RCT: randomised controlled trial

Figure 17: All-cause mortality (non-RCT)

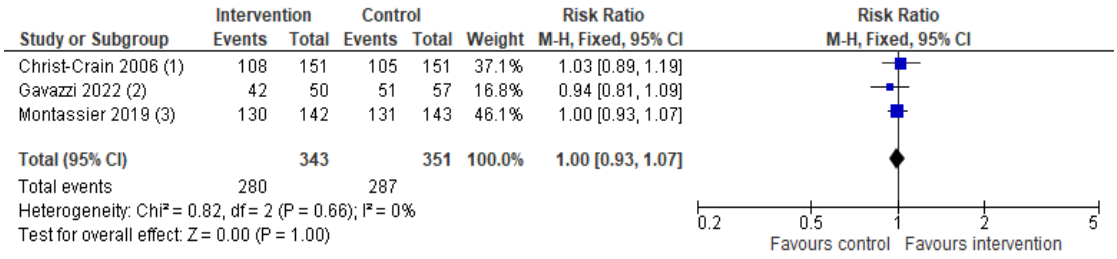
Lower scores favour PCT intervention group



CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin; RCT: randomised controlled trial

Figure 18: Clinical cure

Higher scores favour PCT intervention group



Footnotes
(1) At 6 week follow up. Defined as resolution of clinical, laboratory and radiographic signs of CAP
(2) At 45 day follow-up. Defined as physician judgement: no clinical sign of pneumonia persisted.
(3) At 30 days. Defined as resolution of all CAP symptoms and return to pre-CAP state

CAP: community acquired pneumonia; CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin

Figure 19: Overall adverse outcome (composite measure) (RCT only)

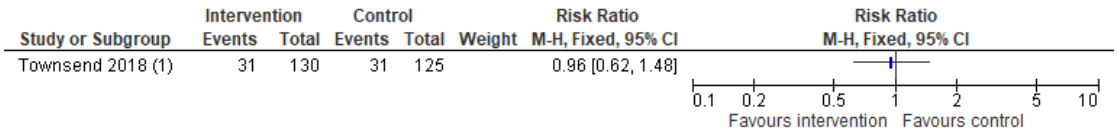
Lower scores favour PCT intervention group

Footnotes
(1) At 6 week follow-up. Defined as death, recurrence, relapse, or persistence of clinical, laboratory and radiographic signs of CAP
(2) Within 30 days. Composite of death, ICU admission, recurrence / rehospitalisation, or disease-specific complication
(3) Within 30 days. Composite of death from any cause, ICU admission, disease-specific complications (e.g. lung abscess or empyema)

CAP: community acquired pneumonia; CI: confidence interval; ICU: intensive care unit; M-H: Mantel–Haenszel; PCT: procalcitonin; RCT: randomised controlled trial

Figure 20: Overall adverse outcome (composite measure) (non-RCT)

Lower scores favour PCT intervention group



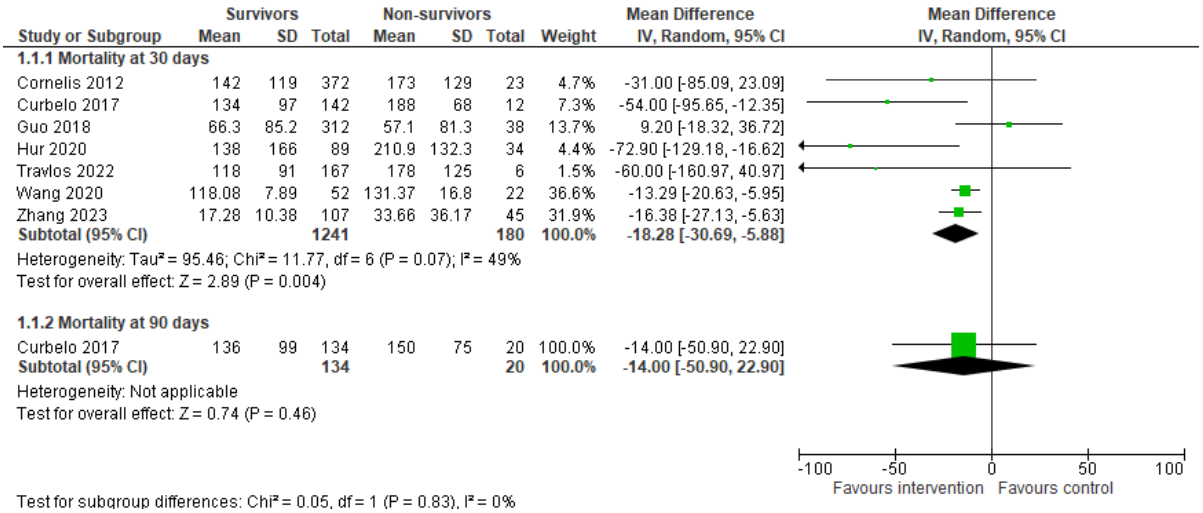
Footnotes
(1) Within 30 days. Composite of new antibiotic prescription for LRTI, transfer to ICU, death, antibiotic side effects, disease-specific...

CI: confidence interval; ICU: intensive care unit; LRTI: lower respiratory tract infection; M-H: Mantel–Haenszel; PCT: procalcitonin; RCT: randomised controlled trial

E.1.2 Prognostic evidence

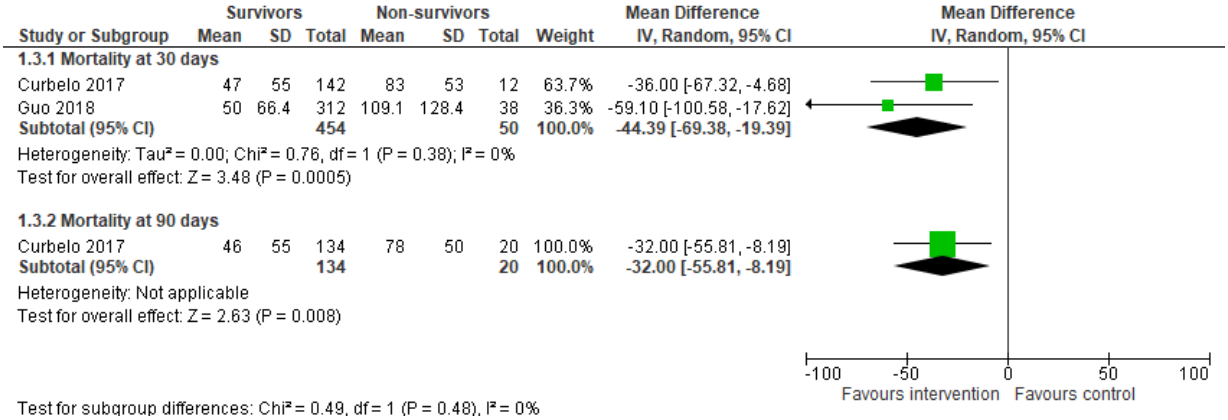
E.1.2.1 C-reactive protein

Figure 21: Admission CRP for survivors and non-survivors



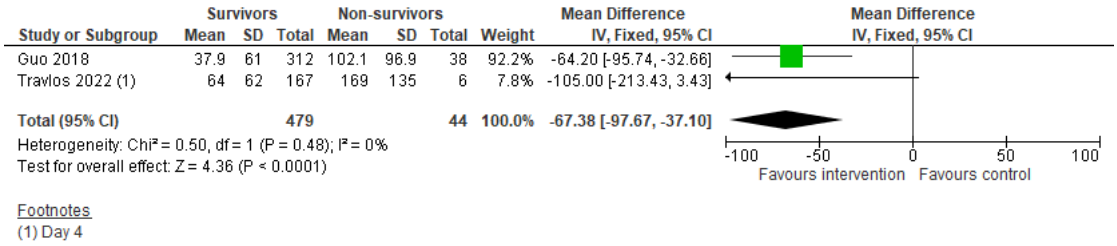
CI: confidence interval; CRP: C-reactive protein; IV: inverse variance; RCT: randomised controlled trial; SD: standard deviation

Figure 22: Day 3 CRP for survivors and non-survivors



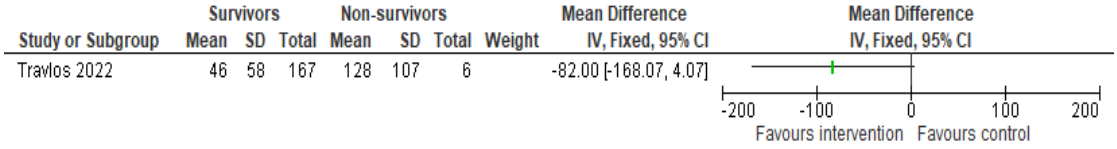
CI: confidence interval; CRP: C-reactive protein; IV: inverse variance; RCT: randomised controlled trial; SD: standard deviation

Figure 23: Day 5 CRP for survivors vs non-survivors



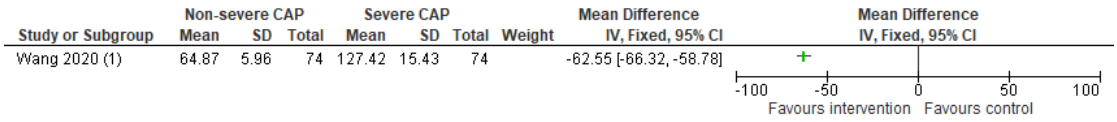
CI: confidence interval; CRP: C-reactive protein; IV: inverse variance; RCT: randomised controlled trial; SD: standard deviation

Figure 24: Day 7 CRP for survivors vs non-survivors



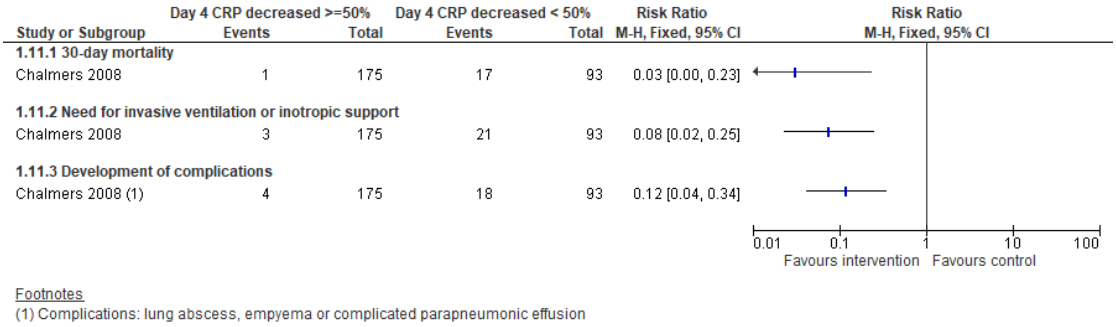
CI: confidence interval; CRP: C-reactive protein; IV: inverse variance; RCT: randomised controlled trial; SD: standard deviation

Figure 25: Admission CRP by CAP severity



CAP: community acquired pneumonia; CI: confidence interval; CRP: C-reactive protein; IV: inverse variance; RCT: randomised controlled trial; SD: standard deviation

Figure 26: Outcomes by CRP decline vs no CRP decline

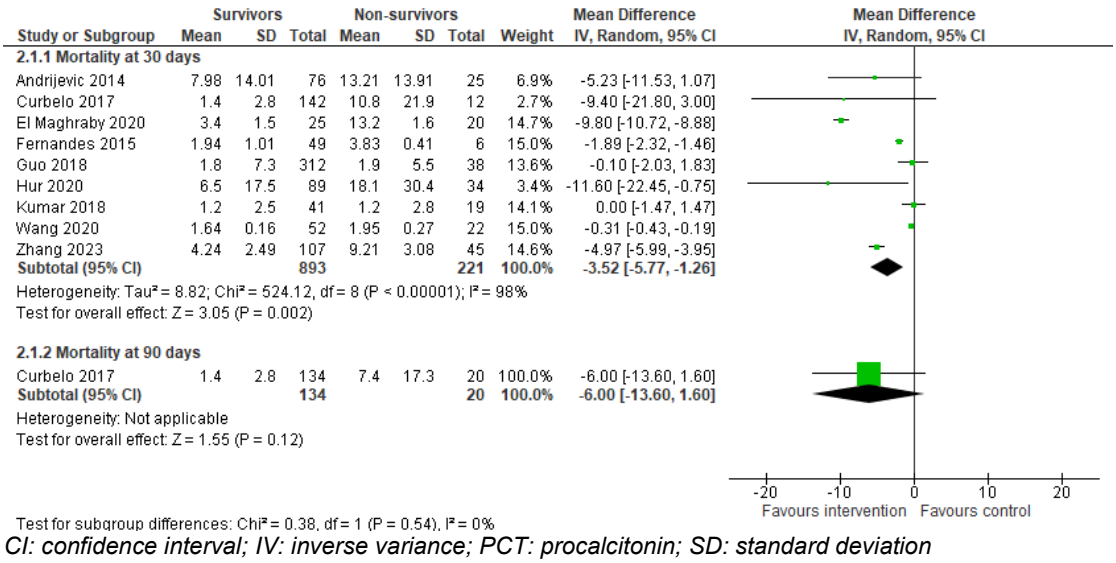


Footnotes
(1) Complications: lung abscess, empyema or complicated parapneumonic effusion

CI: confidence interval; CRP: C-reactive protein; M-H: Mantel–Haenszel; RCT: randomised controlled trial

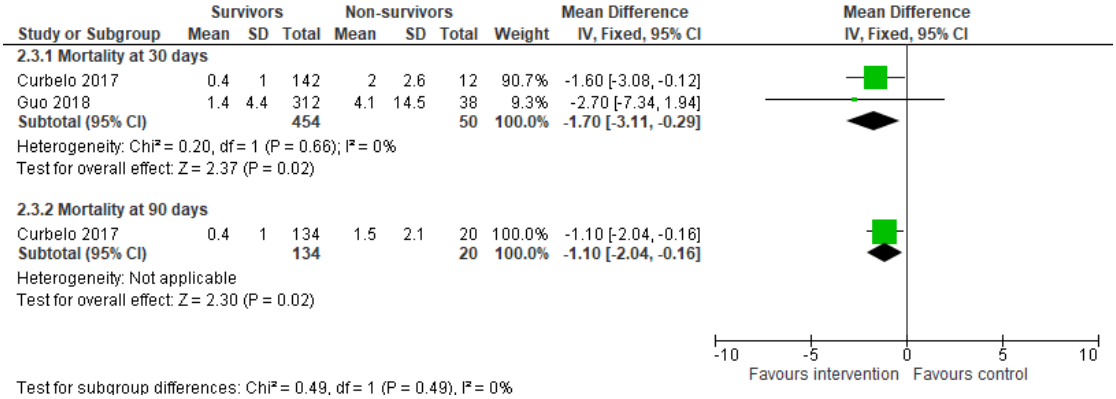
E.1.2.2 Procalcitonin

Figure 27: Admission PCT for survivors vs non-survivors



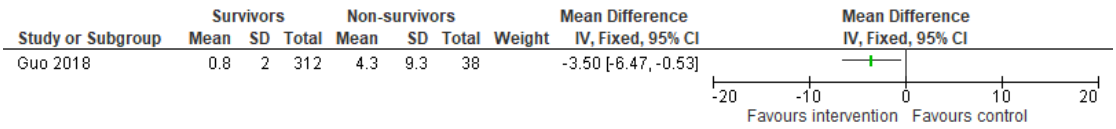
CI: confidence interval; IV: inverse variance; PCT: procalcitonin; SD: standard deviation

Figure 28: Day 3 PCT for survivors vs non-survivors



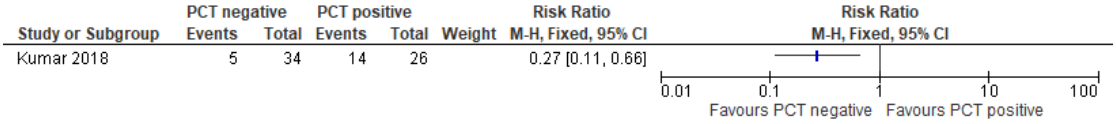
CI: confidence interval; IV: inverse variance; PCT: procalcitonin; SD: standard deviation

Figure 29: Day 5 PCT for survivors vs non-survivors



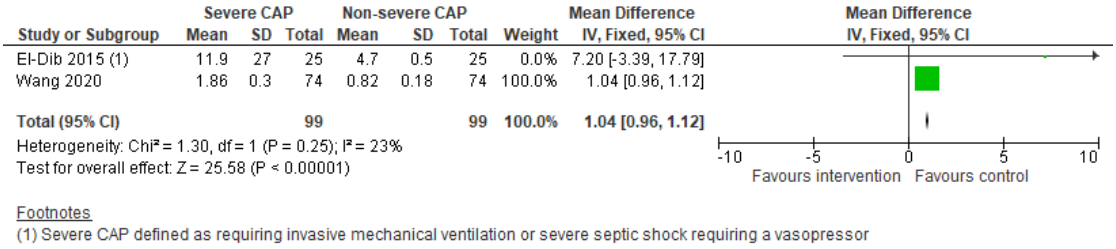
CI: confidence interval; IV: inverse variance; PCT: procalcitonin; SD: standard deviation

Figure 30: Death in PCT positive (>0.5ng/ml) vs PCT negative (≤0.5ng/ml) patients



CI: confidence interval; IV: inverse variance; PCT: procalcitonin; SD: standard deviation

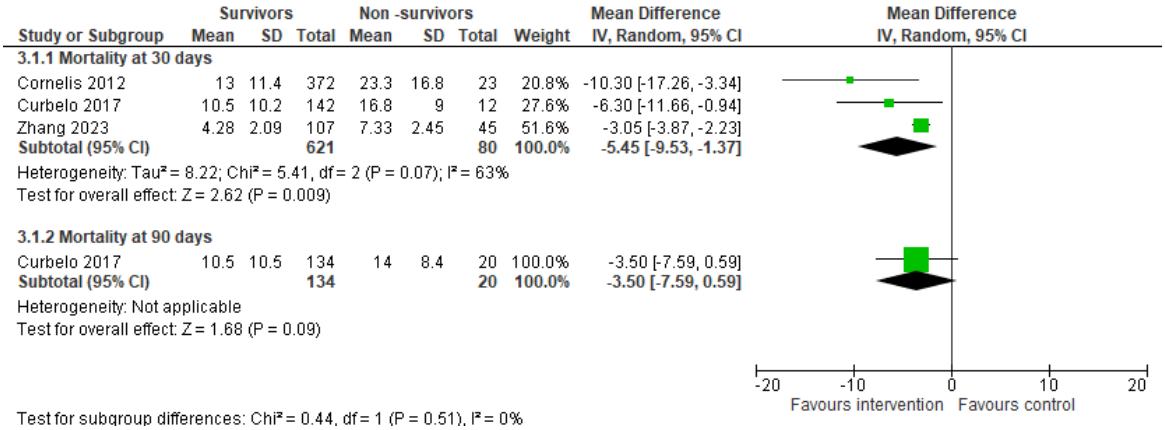
Figure 31: Admission PCT by CAP severity



CAP: community acquired pneumonia; CI: confidence interval; IV: inverse variance; PCT: procalcitonin; SD: standard deviation

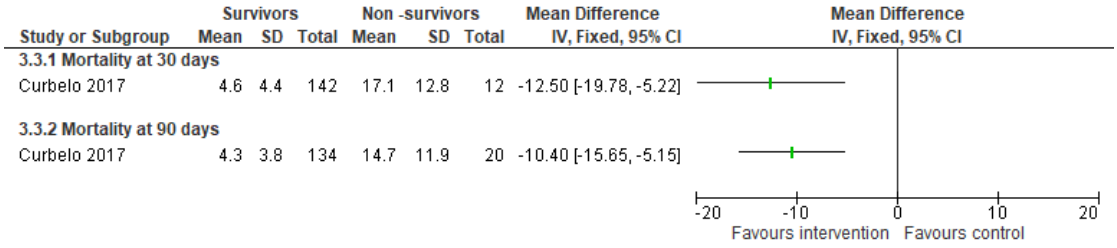
E.1.2.3 Neutrophil to lymphocyte ratio

Figure 32: Admission NLR for survivors vs non-survivors



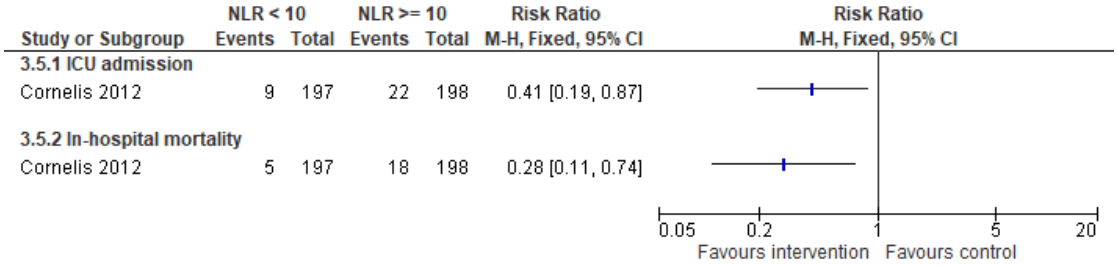
CI: confidence interval; IV: inverse variance; NLR: neutrophil to lymphocyte ratio; SD: standard deviation

Figure 33: Day 3-5 NLR for survivors vs non-survivors



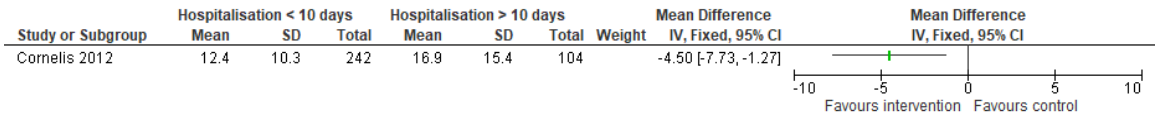
CI: confidence interval; IV: inverse variance; NLR: neutrophil to lymphocyte ratio; SD: standard deviation

Figure 34: Outcomes for admission NLR > 10 vs ≤ 10



CI: confidence interval; ICU: intensive care unit; M-H: Mantel–Haenszel; NLR: neutrophil to lymphocyte ratio

Figure 35: Admission NLR in patients hospitalised for < 10 days vs patients hospitalised for ≥ 10 days



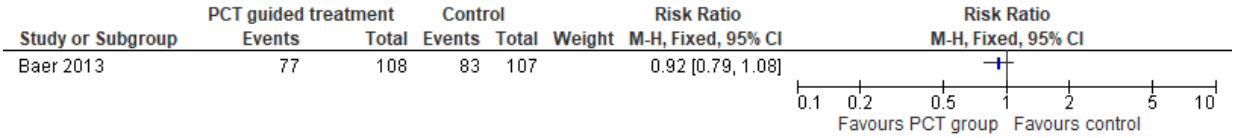
CI: confidence interval; IV: inverse variance; NLR: neutrophil to lymphocyte ratio; SD: standard deviation

E.2 Babies, children and young people

E.2.1 Procalcitonin-guided antibiotic treatment vs usual care in babies, children and young people with pneumonia

Figure 36. Antibiotics prescribed

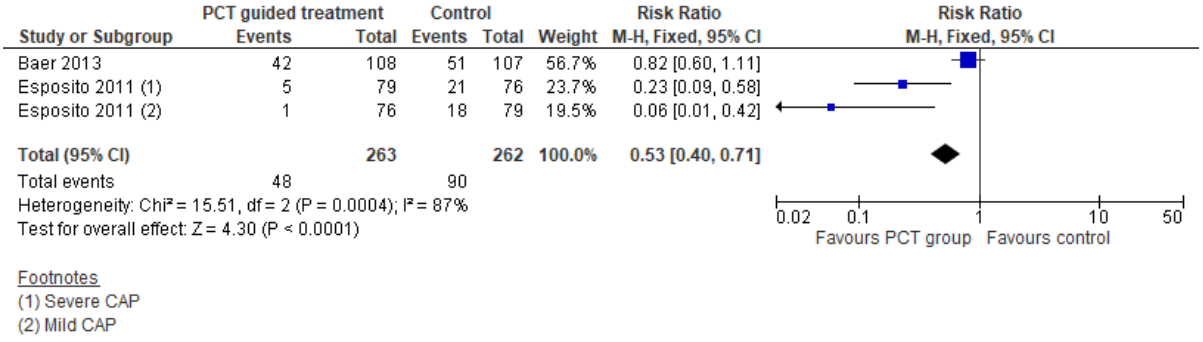
Lower scores favour PCT intervention group



CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin

Figure 37. Antibiotic side effects (rash, nausea, diarrhoea)

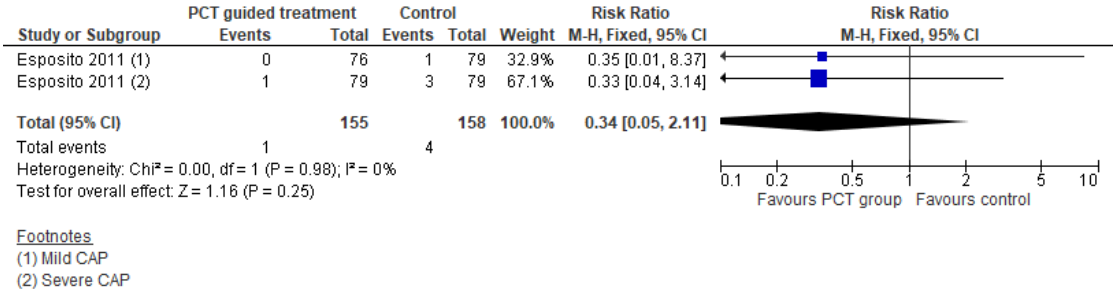
Lower scores favour PCT intervention group



CAP: community acquired pneumonia; CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin

Figure 38. New antibiotic prescription (resumed after discontinuation)

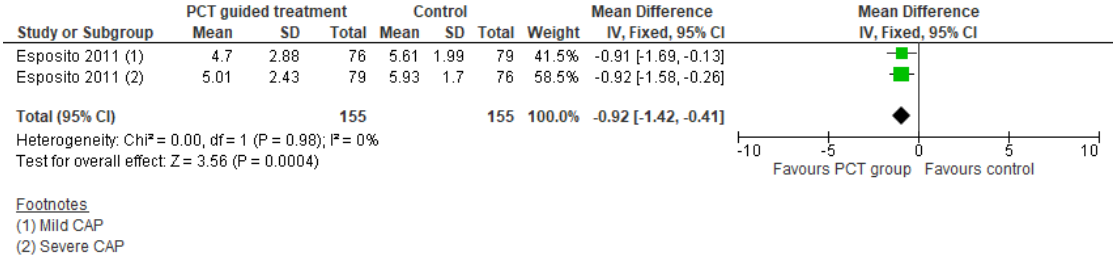
Lower scores favour PCT intervention group



CAP: community acquired pneumonia; CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin

Figure 40. Duration of hospitalisation

Lower scores favour PCT intervention group

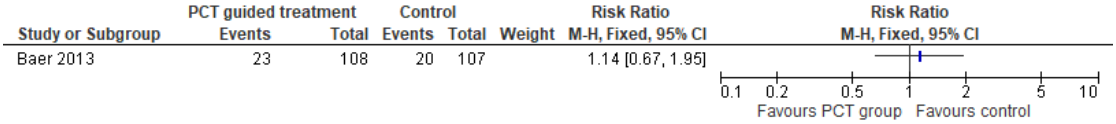


Footnotes
(1) Mild CAP
(2) Severe CAP

CAP: community acquired pneumonia; CI: confidence interval; IV: inverse variance; PCT: procalcitonin; SD: standard deviation

Figure 41. Occurrence of complications, serious adverse events or disease-specific failure

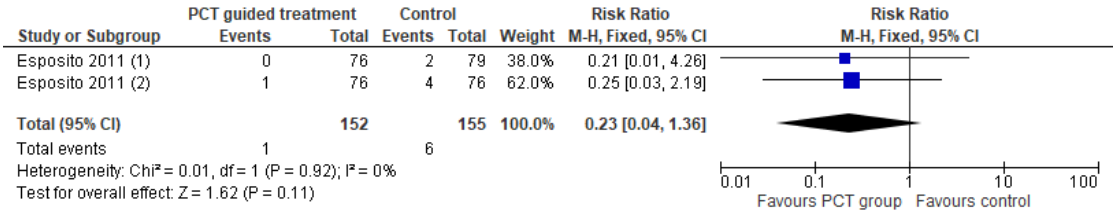
Lower scores favour PCT intervention group



CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin

Figure 42. Recurrence of respiratory symptoms

Lower scores favour PCT intervention group



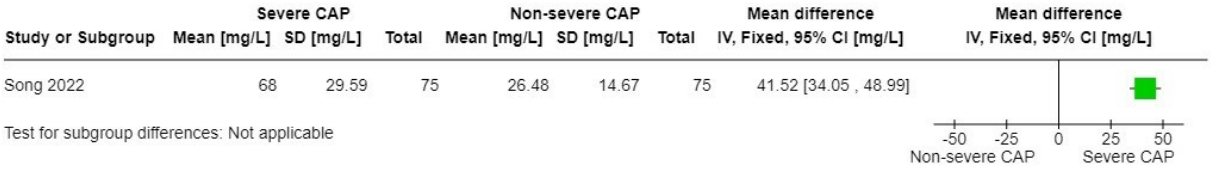
Footnotes
(1) Mild CAP
(2) Severe CAP

CAP: community acquired pneumonia; CI: confidence interval; M-H: Mantel–Haenszel; PCT: procalcitonin

E.2.2 Prognostic evidence

E.2.2.1 C-reactive protein

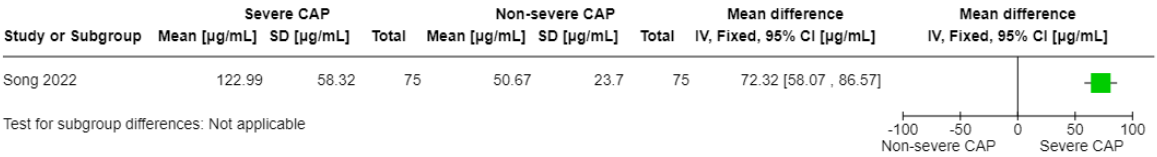
Figure 43. Admission CRP for severe vs non-severe CAP



CAP: community acquired pneumonia; CI: confidence interval; CRP: C-reactive protein; IV: inverse variance; SD: standard deviation

E.2.2.2 Procalcitonin

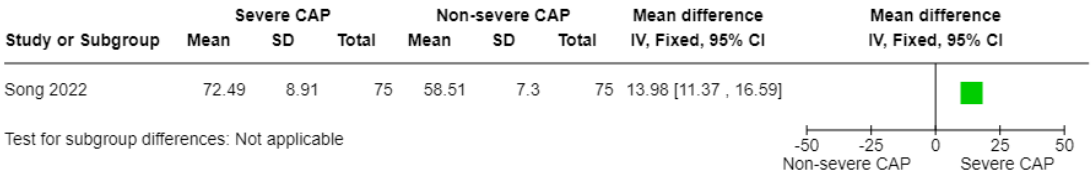
Figure 44. Admission PCT for severe vs non-severe CAP



CAP: community acquired pneumonia; CI: confidence interval; IV: inverse variance; PCT: procalcitonin; SD: standard deviation

E.2.2.3 Neutrophil to lymphocyte ratio

Figure 45. Admission NLR for severe vs non-severe CAP



CAP: community acquired pneumonia; CI: confidence interval; IV: inverse variance; NLR: neutrophil to lymphocyte ratio; SD: standard deviation

Appendix F – GRADE tables

F.1: Adults

F.1.1 Procalcitonin-guided antibiotic treatment vs. control (usual care)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCT-guided antibiotic treatment	Control (usual care)	Relative (95% CI)	Absolute		
Duration of antibiotic therapy (days) MID = 3.25												
1[1]	randomised trials	not serious[a]	serious[b]	not serious[c]	not serious	none	151	151	-	MD **7.1 lower** (8.44 lower to 5.76 lower)	⊕⊕⊕◯ Moderate	CRITICAL
Antibiotic use - antibiotics prescribed												
3[2]	randomised trials	not serious[d]	serious[e]	not serious[c]	not serious	none	670/753 (89.0%)	753/759 (99.2%)	**RR 0.9** (0.87 to 0.92)	**99 fewer per 1,000** (from 79 fewer to 129 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Antibiotic use day 5 to 6												
2[3]	randomised trials	not serious[d]	not serious[f]	not serious[g]	not serious	none	299/510 (58.6%)	478/522 (91.6%)	**RR 0.64** (0.59 to 0.69)	**330 fewer per 1000** (from 284 fewer to 375 fewer)	⊕⊕⊕⊕ High	CRITICAL
Antibiotic use day 7 to 8												
2[3]	randomised trials	not serious[d]	not serious[h]	not serious[g]	not serious	none	203/510 (39.8%)	402/522 (77.0%)	**RR 0.52** (0.46 to 0.58)	**370 fewer per 1000** (from 323 fewer to 416 fewer)	⊕⊕⊕⊕ High	CRITICAL
Antibiotic use after day 13												
1[4]	randomised trials	not serious[a]	serious[b]	not serious[c]	not serious	none	41/460 (8.9%)	91/465 (19.6%)	**RR 0.46** (0.32 to 0.64)	**106 fewer per 1,000** (from 70 fewer to 133 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
New antibiotic prescription after hospitalisation (RCT only)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCT-guided antibiotic treatment	Control (usual care)	Relative (95% CI)	Absolute		
1[5]	randomised trials	serious[i]	serious[b]	not serious[c]	very serious[j]	none	20/142 (14.1%)	15/143 (10.5%)	**RR 1.34** (0.72 to 2.52)	**36 more per 1000** (from 29 fewer to 159 more)	⊕◯◯◯ Very low	CRITICAL
New antibiotic prescription after hospitalisation (non-RCT only)												
1[6]	non-randomised trial	very serious[k]	serious[b]	not serious[c]	very serious[j]	none	10/130 (7.7%)	13/125 (10.4%)	**RR 0.74** (0.34 to 1.62)	**27 fewer per 1000** (69 fewer to 64 more)	⊕◯◯◯ Very low	CRITICAL
Reinitiation of antibiotic therapy within 72 hours of discontinuation												
1[7]	non-randomised trial	very serious[k]	serious[b]	not serious[c]	very serious[j]	none	1/37 (2.7%)	1/37 (2.7%)	**RR 1.00** (0.06 to 15.40)	**0 fewer per 1,000** (from 25 fewer to 389 more)	⊕◯◯◯ Very low	CRITICAL
Pneumonia recurrence after antibiotic discontinuation												
1[8]	non-randomised trial	very serious[k]	serious[b]	not serious[c]	very serious[j]	none	5/116 (4.3%)	7/116 (6.0%)	**RR 0.71** (0.23 to 2.19)	**18 fewer per 1,000** (from 46 fewer to 72 more)	⊕◯◯◯ Very low	CRITICAL
Adverse effects from antibiotic treatment (including nausea, diarrhoea, and rash) (RCT only)												
1[4]	randomised trials	not serious[a]	serious[b]	not serious[c]	serious[l]	none	108/460 (23.5%)	154/465 (33.1%)	**RR 0.71** (0.57 to 0.87)	**96 fewer per 1,000** (from 142 fewer to 43 fewer)	⊕⊕◯◯ Low	IMPORTANT
Adverse effects from antibiotic treatment (including nausea, diarrhoea and rash) (non-RCT only)												
1[6]	non-randomised trial	very serious[k]	serious[b]	not serious[c]	very serious[j]	none	6/130 (4.6%)	4/125 (3.2%)	**RR 1.44** (0.42 to 4.99)	**14 more per 1000** (from 19 fewer to 128 more)	⊕◯◯◯ Very low	IMPORTANT
C. diff infection												
2[9]	non-randomised trials	very serious[k]	not serious[f]	not serious[c]	very serious[j]	none	3/167 (1.8%)	2/162 (1.2%)	**RR 1.47** (0.25 to 8.66)	**6 more per 1000** (from 9 fewer to 95 more)	⊕◯◯◯ Very low	IMPORTANT
Length of hospitalisation. MID = 4.5												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCT-guided antibiotic treatment	Control (usual care)	Relative (95% CI)	Absolute		
1[1]	randomised trials	not serious[a]	serious[b]	not serious[c]	not serious	none	151	151	-	MD **1 lower** (3.04 lower to 1.04 higher)	⊕⊕⊕◯ Moderate	CRITICAL
Need for ICU admission (RCTs only)												
2[10]	randomised trials	serious[i]	not serious[h]	not serious[c]	very serious[j]	none	38/293 (13.0%)	32/294 (10.9%)	**RR 1.19** (0.77 to 1.85)	**21 more per 1000** (from 25 fewer to 93 more)	⊕◯◯◯ Very low	CRITICAL
Need for ICU admission (non-RCTs only)												
1[6]	non-randomised trials	very serious[k]	serious[b]	not serious[c]	very serious[j]	none	10/130 (7.7%)	8/125 (6.4%)	**RR 1.2** (0.49 to 2.95)	**13 more per 1000** (from 33 fewer to 125 more)	⊕◯◯◯ Very low	CRITICAL
All-cause mortality (RCTs only)												
4[11]	randomised trials	not serious[d]	not serious[f]	not serious[g]	very serious[j]	none	52/803 (6.5%)	55/816 (6.7%)	**RR 0.97** (0.67 to 1.39)	**2 fewer per 1000** (from 22 fewer to 26 more)	⊕⊕◯◯ Low	CRITICAL
All-cause mortality (non-RCTs only)												
3[12]	non-randomised trials	very serious[k]	not serious[f]	not serious[c]	very serious[j]	none	8/283 (2.8%)	9/278 (3.2%)	**RR 0.86** (0.34 to 2.19)	**5 fewer per 1000** (from 21 fewer to 39 more)	⊕◯◯◯ Very low	CRITICAL
Clinical cure												
3[13]	randomised trials	serious[i]	not serious[f]	not serious[g]	not serious	none	280/343 (81.6%)	287/351 (81.8%)	**RR 1.00** (0.93 to 1.07)	**0 fewer per 1000** (from 57 fewer to 57 more)	⊕⊕⊕◯ Moderate	CRITICAL
Overall adverse outcome (composite measure) (RCTs only)												
3[2]	randomised trials	not serious[d]	not serious[f]	not serious[c]	serious[l]	none	120/753 (15.9%)	150/759 (19.8%)	**RR 0.81** (0.65 to 1)	**38 fewer per 1000** (from 69 fewer to 0 more)	⊕⊕⊕◯ Moderate	CRITICAL
Overall adverse outcome (composite measure) (non-RCTs only)												
1[6]	non-randomised trials	very serious[k]	serious[b]	not serious[c]	very serious[j]	none	31/130 (23.8%)	31/125 (24.8%)	**RR 0.96** (0.62 to 1.48)	**10 fewer per 1000** (from 94 fewer to 119 more)	⊕◯◯◯ Very low	CRITICAL

CI: confidence interval; ICU: intensive care unit; MD: mean difference; PCT: procalcitonin; RCT: randomized controlled trial; RR: risk ratio
[a] Not downgraded: study at low risk of bias
[b] Downgraded once for inconsistency: single study
[c] Not downgraded: studies directly applicable
[d] Not downgraded: less than 33.3% of the weight in the meta-analysis came from studies at moderate or high risk of bias
[e] Downgraded once as I^2 between 33.3% and 66.7% (I^2 = 40%)
[f] Not downgraded: I^2 = 0%
[g] Not downgraded: more than 33.3% of the weight in the meta-analysis came from directly applicable studies
[h] Not downgraded: I^2 < 33.3%
[i] Downgraded once as greater than 33.3% of the weight in the meta-analysis came from studies at moderate risk of bias
[j] Downgraded twice as 95%CI crosses two clinical decision thresholds (0.8 and 1.25)
[k] Downgraded twice: non-randomised study at moderate risk of bias
[l] Downgraded once as 95%CI crosses one clinical decision threshold (0.8)

1 Christ-Crain 2006
2 Christ-Crain 2006, Montassier 2019, Schuetz 2009
3 Gavazzi 2022, Schuetz 2009
4 Schuetz 2009
5 Montassier 2019
6 Townsend 2018
7 Subedi 2020
8 Akagi 2019
9 Subedi 2020, Townsend 2018
10 Christ-Crain 2006, Montassier 2019
11 Christ-Crain 2006, Gavazzi 2022, Montassier 2019, Schuetz 2009
12 Akagi 2019, Subedi 2020, Townsend 2018
13 Christ-Crain 2006, Gavazzi 2022, Montassier 2019

F.1.2 Prognostic evidence for C-reactive protein

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**C-Reactive Protein**	**Control**	**Relative (95% CI)**	**Absolute**		
Admission CRP for survivors and non-survivors - Mortality at 30 days. MID = 42.04 (Better indicated by lower values)												
7[1]	observational studies	no serious risk of bias	serious[a]	no serious indirectness	no serious imprecision	none	1241	180	-	MD 18.28 lower (30.69 to 5.88 lower)	⊕OOO VERY LOW	
Admission CRP for survivors and non-survivors - Mortality at 90 days. MID = 37.5 (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	C-Reactive Protein	Control	Relative (95% CI)	Absolute		
1[2]	observational studies	serious risk of bias[h]	serious[b]	no serious indirectness	serious[c]	none	134	20	-	MD 14 lower (50.9 lower to 22.9 higher)	⊕OOO VERY LOW	
Day 3 CRP for survivors vs non-survivors - Mortality at 30 days. MID = 58.6 (Better indicated by lower values)												
2[3]	observational studies	serious risk of bias[i]	no serious inconsistency	no serious indirectness	serious[d]	none	454	50	-	MD 44.39 lower (69.38 to 19.39 lower)	⊕OOO VERY LOW	
Day 3 CRP for survivors vs non-survivors - Mortality at 90 days. MID = 25 (Better indicated by lower values)												
1[2]	observational studies	serious risk of bias[h]	serious[2]	no serious indirectness	serious[e]	none	134	20	-	MD 32 lower (55.81 to 8.19 lower)	⊕OOO VERY LOW	
Day 5 CRP for survivors vs non-survivors (mortality at 30 days). MID = 57.9 (Better indicated by lower values)												
2[4]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[f]	none	479	44	-	MD 67.38 lower (97.67 to 37.1 lower)	⊕OOO VERY LOW	
Day 7 CRP for survivors vs non-survivors (mortality at 30 days). MID = 53.5. (Better indicated by lower values)												
1[5]	observational studies	no serious risk of bias	serious[b]	no serious indirectness	serious[g]	none	167	6	-	MD 82 lower (168.07 lower to 4.07 higher)	⊕OOO VERY LOW	
Admission CRP by CAP severity. MID = 7.72. (Better indicated by lower values)												
1[6]	observational studies	no serious risk of bias	serious[b]	no serious indirectness	no serious imprecision	none	74	74	-	MD 62.55 lower (66.32 to 58.78 lower)	⊕OOO VERY LOW	
Day 4 CRP decrease by >=50% vs Day 4 CRP increase or decrease by < 50% - 30-day mortality												
1[7]	observational studies	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	1/175 (0.57%)	17/93 (18.3%)	RR 0.03 (0 to 0.23)	177 fewer per 1000 (from 141 fewer to 183 fewer)	⊕OOO VERY LOW	
Day 4 CRP decrease by >=50% vs Day 4 CRP increase or decrease by < 50% - Need for invasive ventilation or inotropic support												
1[7]	observational studies	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	3/175 (1.7%)	21/93 (22.6%)	RR 0.08 (0.02 to 0.25)	208 fewer per 1000 (from 169 fewer to 221 fewer)	⊕OOO VERY LOW	
Day 4 CRP decrease by >=50% vs Day 4 CRP increase or decrease by < 50% - Development of complications												
1[7]	observational studies	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	4/175 (2.3%)	18/93 (19.4%)	RR 0.12 (0.04 to 0.34)	170 fewer per 1000 (from 128 fewer to 186 fewer)	⊕OOO VERY LOW	

CAP: community acquired pneumonia; CI: confidence interval; CRP: C-reactive protein; MD: mean difference; MID: minimally important difference; RR: risk ratio
[a] Downgraded once as I2 was between 33.3% and 66.7% (I2 = 49%)
[b] Downgraded once - single study
[c] Downgraded once as 95%CI crosses one calculated MID (35.7)
[d] Downgraded once as 95% CI crosses one calculated MID (58.6)
[e] Downgraded once as 95%CI crosses one calculated MID (25)
[f] Downgraded once as 95%CI crosses one calculated MID (57.9)
[g] Downgraded once as 95%CI crosses one calculated MID (53.5)
[h] Downgraded once as study rated as moderate risk of bias (no baseline sample characteristics reported)
[i] Downgraded once as >33.3% of the weight in the meta-analyses came from a study at moderate risk of bias (no baseline sample characteristics reported)

1 Cornelis 2012, Curbelo 2017, Guo 2018, Hur 2020, Travlos 2022, Wang 2020, Zhang 2023
2 Curbelo 2017
3 Curbelo 2017, Guo 2018
4 Guo 2018, Travlos 2022
5 Travlos 2022
6 Wang 2020
7 Chalmers 2008

F.1.3 Prognostic evidence for Procalcitonin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Procalcitonin (PCT)	Control	Relative (95% CI)	Absolute		
Admission PCT for survivors vs non-survivors - Mortality at 30 days. MID = 4.44 (Better indicated by lower values)												
9[1]	observational studies	no serious risk of bias	very serious[a]	no serious indirectness	serious[b]	none	893	221	-	MD 3.52 lower (5.77 to 1.26 lower)	⊕OOO VERY LOW	
Admission PCT for survivors vs non-survivors - Mortality at 90 days. MID = 8.65 (Better indicated by lower values)												
1[2]	observational studies	no serious risk of bias	serious[c]	no serious indirectness	serious[d]	none	134	20	-	MD 6 lower (13.6 lower to 1.6 higher)	⊕OOO VERY LOW	
Day 3 PCT for survivors vs non-survivors - Mortality at 30 days. MID = 4.28 (Better indicated by lower values)												
2[3]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	454	50	-	MD 1.7 lower (3.11 to 0.29 lower)	⊕⊕OO LOW	
Day 3 PCT for survivors vs non-survivors - Mortality at 90 days. MID = 1.05 (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Procalcitonin (PCT)	Control	Relative (95% CI)	Absolute		
1[2]	observational studies	no serious risk of bias	serious[c]	no serious indirectness	serious[e]	none	134	20	-	MD 1.1 lower (2.04 to 0.16 lower)	⊕OOO VERY LOW	
Day 5 PCT for survivors vs non-survivors – Mortality at 30 days. MID = 4.65 (Better indicated by lower values)												
1[4]	observational studies	no serious risk of bias	serious[c]	no serious indirectness	serious[f]	none	312	38	-	MD 3.5 lower (6.47 to 0.53 lower)	⊕OOO VERY LOW	
Death in PCT positive (>0.5ng/ml) vs PCT negative (≤0.5ng/ml) patients												
1[5]	observational studies	no serious risk of bias	serious[c]	no serious indirectness	no serious imprecision	none	5/34 (14.7%)	14/26 (53.8%)	RR 0.27 (0.11 to 0.66)	393 fewer per 1000 (183 fewer to 479 fewer)	⊕OOO VERY LOW	
Admission PCT by CAP severity. MID = 0.17 (Better indicated by lower values)												
2[6]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	99	99	-	MD 1.04 higher (0.96 to 1.12 higher)	⊕⊕OO LOW	

CAP: community acquired pneumonia; CI: confidence interval; MD: mean difference; MID: minimally important difference; PCT: procalcitonin

[a] Downgraded twice as I2 was greater than 66.7% (I2 = 98%)
[b] Downgraded once as 95%CI crosses one calculated MID (4.44)
[c] Downgraded once – single study
[d] Downgraded once as 95%CI crosses one calculated MID (8.65)
[e] Downgraded once as 95%CI crosses one calculated MID (1.05)
[f] Downgraded once as 95%CI crosses one calculated MID (4.65)

1 Andrijevic 2014, Curbelo 2017, El Maghraby 2020, Fernandes 2015, Guo 2018, Hur 2020, Kumar 2018, Wang 2020, Zhang 2023
2 Curbelo 2017
3 Curbelo 2017, Guo 2018
4 Guo 2018
5 Kumar 2018
6 El-Dib 2015, Wang 2020

F.1.4 Prognostic evidence for Neutrophil to lymphocyte ratio

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neutrophil to lymphocyte ratio (NLR)	Control	Relative (95% CI)	Absolute		

Admission NLR for survivors vs non-survivors - Mortality at 30 days. MID = 4.71 (Better indicated by lower values)												
3[1]	observational studies	no serious risk of bias	serious[a]	no serious indirectness	serious[b]	none	621	80	-	MD 5.45 lower (9.53 to 1.37 lower)	⊕OOO VERY LOW	
Admission NLR for survivors vs non-survivors - Mortality at 90 days. MID = 4.2 (Better indicated by lower values)												
1[2]	observational studies	no serious risk of bias	serious[c]	no serious indirectness	serious[d]	none	134	20	-	MD 3.5 lower (7.59 lower to 0.59 higher)	⊕OOO VERY LOW	
Day 3-5 NLR for survivors vs non-survivors - Mortality at 30 days. MID = 6.4 (Better indicated by lower values)												
1[2]	observational studies	no serious risk of bias	serious[c]	no serious indirectness	serious[e]	none	142	12	-	MD 12.5 lower (19.78 to 5.22 lower)	⊕OOO VERY LOW	
Day 3-5 NLR for survivors vs non-survivors - Mortality at 90 days. MID = 5.95 (Better indicated by lower values)												
1[2]	observational studies	no serious risk of bias	serious[c]	no serious indirectness	serious[f]	none	134	20	-	MD 10.4 lower (15.65 to 5.15 lower)	⊕OOO VERY LOW	
Admission NLR < 10 or >=10 - ICU admission												
1[3]	observational studies	no serious risk of bias	serious[c]	no serious indirectness	serious[g]	none	9/197 (4.6%)	22/198 (11.1%)	RR 0.41 (0.19 to 0.87)	66 fewer per 1000 (from 14 fewer to 90 fewer)	⊕OOO VERY LOW	
Admission NLR < 10 or >=10 - In-hospital mortality												
1[3]	observational studies	no serious risk of bias	serious[c]	no serious indirectness	no serious imprecision	none	5/197 (2.5%)	18/198 (9.1%)	RR 0.28 (0.11 to 0.74)	65 fewer per 1000 (from 24 fewer to 81 fewer)	⊕OOO VERY LOW	
Admission NLR in patients hospitalised for <10 days vs patients hospitalised for ≥10 days. MID = 7.7 (Better indicated by lower values)												
1[3]	observational studies	no serious risk of bias	serious[c]	no serious indirectness	serious[8]	none	242	104	-	MD 4.5 lower (7.73 to 1.27 lower)	⊕OOO VERY LOW	

CI: confidence interval; ICU: intensive care unit; MD: mean difference; MID: minimally important difference; NLR: neutrophil to lymphocyte ratio; RR: risk ratio

[a] Downgraded once as I2 was between 33.3% and 66.7% (I2 = 63%)
[b] Downgraded once as 95%CI crosses one calculated MID (4.71)
[c] Downgraded once – single study
[d] Downgraded once as 95%CI crosses one calculated MID (4.2)
[e] Downgraded once as 95%CI crosses one calculated MID (6.4)
[f] Downgraded once as 95%CI crosses one calculated MID (5.95)
[g] Downgraded once as 95%CI crosses one clinical MID (0.8)
[h] Downgraded once as 95% CI crosses one calculated (7.7)

1 Cornelis 2012, Curbelo 2017, Zhang 2023
2 Curbelo 2017
3 Cornelis 2012

F.2 Babies, children and young people

F.2.1 Procalcitonin-guided antibiotic treatment vs. control (usual care)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**PCT-guided antibiotic treatment**	**Usual care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Antibiotic prescription												
1[1]	randomised trials	serious[a]	serious[b]	serious[h]	serious[c]	none	77/108 (71.3%)	83/107 (77.6%)	**RR 0.92** (0.79 to 1.08)	**62 fewer per 1,000** (from 163 fewer to 62 more)	⊕◯◯◯ Very low	CRITICAL
Antibiotic side effects												
2[2]	randomised trials	serious[d]	very serious[e]	serious[i]	not serious	none	48/263 (18.3%)	90/262 (34.4%)	**RR 0.53** (0.40 to 0.71)	**161 fewer per 1,000** (from 206 fewer to 100 fewer)	⊕◯◯◯ Very low	IMPORTANT
New antibiotic prescription (resumed after discontinuation)												
1[3]	randomised trials	serious[f]	serious[b]	not serious	very serious[g]	none	1/155 (0.6%)	4/158 (2.5%)	**RR 0.34** (0.05 to 2.11)	**17 fewer per 1,000** (from 24 fewer to 28 more)	⊕◯◯◯ Very low	CRITICAL
Duration of hospitalisation (MID = 1.84)												
1[3]	randomised trials	serious[a]	serious[b]	not serious	not serious	none	155	155	-	MD **0.92 lower** (1.42 lower to 0.41 lower)	⊕⊕◯◯ Low	CRITICAL
Occurrence of complications, serious adverse events or disease-specific failure												
1[1]	randomised trials	serious[a]	serious[b]	serious[h]	very serious[g]	none	23/108 (21.3%)	20/107 (18.7%)	**RR 1.14** (0.67 to 1.95)	**26 more per 1,000** (from 62 fewer to 178 more)	⊕◯◯◯ Very low	CRITICAL
Recurrence of respiratory symptoms												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**PCT-guided antibiotic treatment**	**Usual care**	**Relative (95% CI)**	**Absolute (95% CI)**		
1[3]	randomised trials	serious[f]	serious[b]	not serious	very serious[g]	none	1/152 (0.7%)	6/155 (3.9%)	**RR 0.23** (0.04 to 1.36)	**30 fewer per 1,000** (from 37 fewer to 14 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; MD: mean difference; PCT: procalcitonin; RR: risk ratio

[a] Downgraded once due to moderate risk of bias (outcome measurement relied on self-assessment and patient/caregiver diary entries)
[b] Downgraded once - single study
[c] Downgraded once as 95%CI crosses one clinical decision threshold (0.8)
[d] Downgraded once as greater than 33.3% of the weight in the meta-analysis came from studies at moderate risk of bias
[e] Downgraded twice as I2 was greater than 66.7% (I2 = 87%)
[f] Downgraded once due to moderate risk of bias (trial not registered)
[g] Downgraded twice as 95%CI crosses two clinical decision thresholds (0.8 and 1.25)
[h] Downgraded once as study was partially applicable (only 48% of children here hospitalised)
[i] Downgraded once as >33.3% of the weight in the meta-analysis came from a study rated as partially applicable
[j] Downgraded once

1 Baer 2013
2 Baer 2013, Esposito 2011
3 Esposito 2011

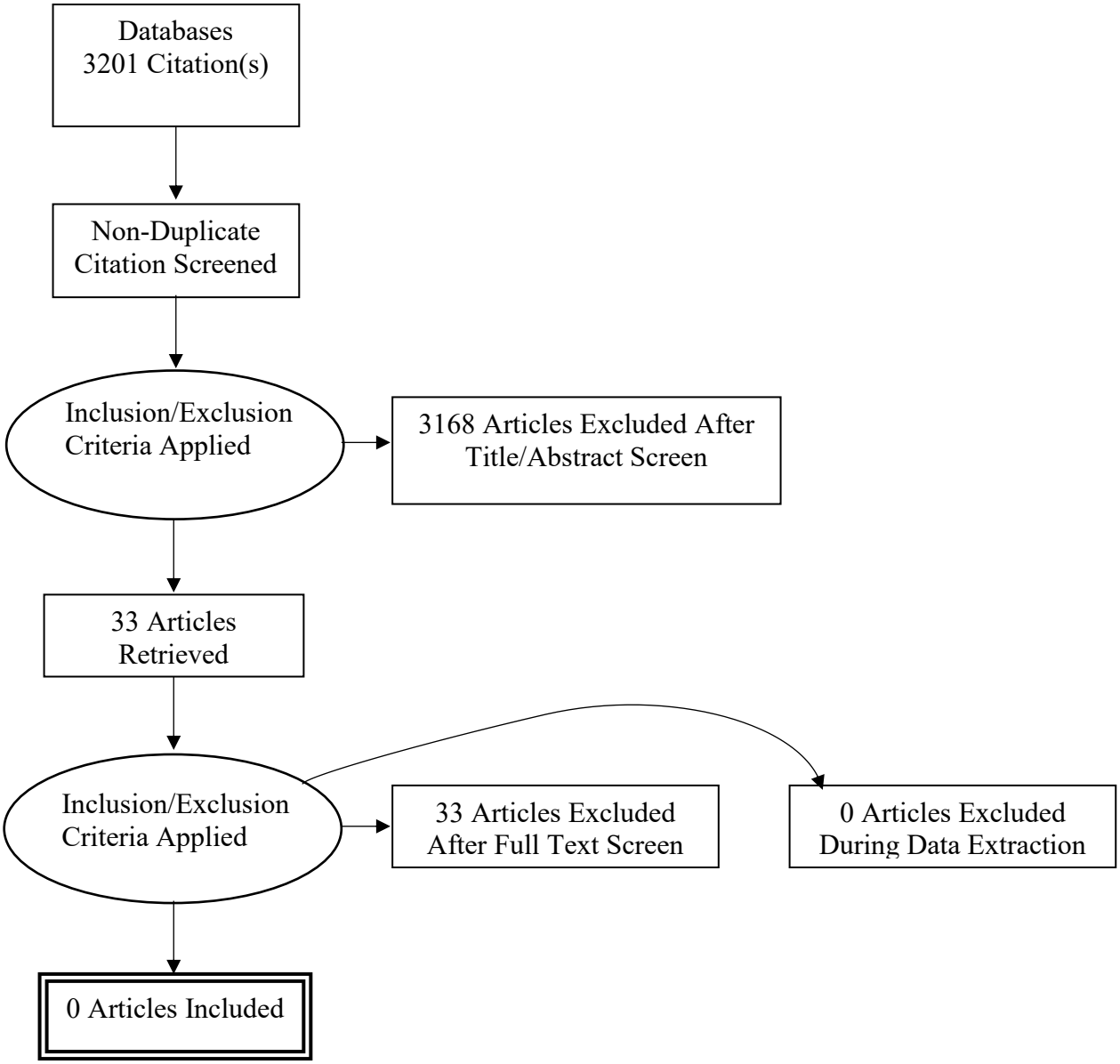
F.2.2 Prognostic evidence for biomarkers at admission

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bio-markers		Relative (95% CI)	Absolute (95% CI)		
Admission CRP by CAP severity. MID = 7.34												
1[1]	non-randomised studies	serious[a]	serious[b]	not serious	not serious	none	75	75	-	MD **41.52 higher** (34.05 higher to 48.99 higher)	⊕◯◯◯ Very low	CRITICAL
Admission Procalcitonin by CAP severity. MID = 11.85												
1[1]	non-randomised studies	serious[a]	serious[b]	not serious	not serious	none	75	75	-	MD **72.32 higher** (58.07 higher to 86.57 higher)	⊕◯◯◯ Very low	CRITICAL
Admission Neutrophil to lymphocyte ratio by CAP severity. MID = 3.65												
1[1]	non-randomised studies	serious[a]	serious[b]	not serious	not serious	none	75	75	-	MD **13.98 higher** (11.37 higher to 16.59 higher)	⊕◯◯◯ Very low	CRITICAL

[a] Downgraded once for moderate risk of bias - no information on inclusion criteria for age; states only 'children'
[b] Downgraded once - single study

1 Song 2022

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No studies were included in this review question.

Appendix I – Health economic model

No health economic modelling was undertaken for this evidence review.

Appendix J – Excluded studies

Clinical studies

J.1 Adults

Effectiveness studies

Study	Code [Reason]
Alzoubi, Osama and Khanfar, Asim (2021) Association between neutrophil to lymphocyte ratio and mortality among community acquired pneumonia patients: a meta-analysis. Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace 92(3)	- Systematic review used as source of primary studies
August, B.A., Kale-Pradhan, P.B., Giuliano, C. et al. (2023) Biomarkers in the intensive care setting: A focus on using procalcitonin and C-reactive protein to optimize antimicrobial duration of therapy. Pharmacotherapy 43(9): 935-949	- Systematic review used as source of primary studies
Branche, Angela, Neeser, Olivia, Mueller, Beat et al. (2019) Procalcitonin to guide antibiotic decision making. Current opinion in infectious diseases 32(2): 130-135	- Systematic review used as source of primary studies
Chen, L Feng, C Dong, J Zhai, YZ Chen, X Li, B Zhou, X Chen, W Li, TS (2016) Procalcitonin levels correlates with the pathogeny and severity of community acquired pneumonia: a meta-analysis. INTERNATIONAL JOURNAL OF CLINICAL AND EXPERIMENTAL MEDICINE 9(7): 13763 - 13772	- Systematic review used as source of primary studies
Dai, BQ; Yuan, XT; Liu, JM (2015) Value of serum procalcitonin for the guidance of antibiotic therapy in children with lower respiratory tract infection. Zhongguo dang dai er ke za zhi [Chinese journal of contemporary pediatrics] 17(12): 1292-1296	- Study not reported in English
Hamade, B. and Huang, D.T. (2020) Procalcitonin: Where Are We Now?. Critical Care Clinics 36(1): 23-40	- Systematic review used as source of primary studies *Narrative review, checked for possible includes*
Heilmann, E., Gregoriano, C., Annane, D. et al. (2021) Duration of antibiotic treatment using procalcitonin-guided treatment algorithms in older patients: A patient-level	- Systematic review used as source of primary studies

Study	Code [Reason]
meta-analysis from randomized controlled trials. Age and Ageing 50(5): 1546-1556	
Hey, J., Thompson-Leduc, P., Kirson, N.Y. et al. (2018) Procalcitonin guidance in patients with lower respiratory tract infections: A systematic review and meta-analysis. Clinical Chemistry and Laboratory Medicine 56(8): 1200-1209	- Systematic review used as source of primary studies
Julian-Jimenez, Agustin; Gonzalez Del Castillo, Juan; Candel, Francisco Javier (2017) Usefulness and prognostic value of biomarkers in patients with community-acquired pneumonia in the emergency department. Medicina clinica 148(11): 501-510	- Study not reported in English
Khan, Faheem, Owens, Mark B, Restrepo, Marcos et al. (2017) Tools for outcome prediction in patients with community acquired pneumonia. Expert review of clinical pharmacology 10(2): 201-211	- Systematic review used as source of primary studies
Kuikel, Sandip, Pathak, Nibesh, Poudel, Sagar et al. (2022) Neutrophil-lymphocyte ratio as a predictor of adverse outcome in patients with community-acquired pneumonia: A systematic review. Health science reports 5(3): e630	- Systematic review used as source of primary studies
Kumar, S., Jan, R.A., Rasool, R. et al. (2018) Utility of procalcitonin in the management of hospital-acquired pneumonia - A review. Current Respiratory Medicine Reviews 14(1): 42-47	- Systematic review used as source of primary studies
Liu, Dan, Su, Long-Xiang, Guan, Wei et al. (2016) Prognostic value of procalcitonin in pneumonia: A systematic review and meta-analysis. Respirology (Carlton, Vic.) 21(2): 280-8	- Systematic review used as source of primary studies
Meier, Marc A, Branche, Angela, Neeser, Olivia L et al. (2019) Procalcitonin-guided Antibiotic Treatment in Patients With Positive Blood Cultures: A Patient-level Meta-analysis of Randomized Trials. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 69(3): 388-396	- Systematic review used as source of primary studies
Pieralli, F., Vannucchi, V., Silverii, M.V. et al. (2016) The real life application of a procalcitonin-based algorithm to reduce	- Not a relevant study design *Case control study, but decision over whether patient was assigned to case or*

Study	Code [Reason]
antibiotic exposure in hospitalized patients with Community acquired pneumonia: A proof of concept. Italian Journal of Medicine 10(3): 213-218	*control group was made by attending physician, and the two groups were not comparable at baseline (case group had admission PCT of 12.1; control group was 1.4, suggesting very significant differences in PCT levels before implementing algorithm).*
Sager, Ramon, Kutz, Alexander, Mueller, Beat et al. (2017) Procalcitonin-guided diagnosis and antibiotic stewardship revisited. BMC medicine 15(1): 15	- Systematic review used as source of primary studies *SR checked for possible primary study includes*
Schuetz, P Christ-Crain, M Thomann, R Falconnier, C Wolbers, M Widmer, I Neidert, S Fricker, T Blum, C Schild, U Regez, K Schoenenberger, R Henzen, C Bregenzer, T Hoess, C Krause, M Bucher, HC Zimmerli, W Mueller, B (2009) Effect of Procalcitonin-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections The ProHOSP Randomized Controlled Trial. JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 302(10): 1059 - 1066	- Duplicate paper
Schuetz, P Wirz, Y Sager, R Christ-Crain, M Stolz, D Tamm, M Bouadma, L Luyt, CE Wolff, M Chastre, J Tubach, F Kristoffersen, KB Burkhardt, O Welte, T Schroeder, S Nobre, V Wei, L Bucher, HC Annane, D Reinhart, K Falsey, AR Branche, A Damas, P Nijsten, M de Lange, DW Deliberato, RO Oliveira, CF Maravic-Stojkovic, V Verduri, A Beghé, B Cao, B Shehabi, Y Jensen, JUS Corti, C van Oers, JAH Beishuizen, A Girbes, ARJ de Jong, E Briel, M Mueller, B (2018) Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. LANCET INFECTIOUS DISEASES 18(1): 95 - 107	- Systematic review used as source of primary studies
Schuetz, P., Wirz, Y., Sager, R. et al. (2017) Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database of Systematic Reviews 2017(10): cd007498	- Systematic review used as source of primary studies
Schuetz, Philipp, Bolliger, Rebekka, Merker, Meret et al. (2018) Procalcitonin-guided antibiotic therapy algorithms for different types of acute respiratory infections based on previous trials. Expert review of anti-infective therapy 16(7): 555-564	- Systematic review used as source of primary studies

Study	Code [Reason]
Shaddock, Erica J (2016) How and when to use common biomarkers in community-acquired pneumonia. Pneumonia (Nathan Qld.) 8: 17	- Systematic review used as source of primary studies
Soni, NJ Samson, DJ Galaydick, JL Vats, V Huang, ES Aronson, N Pitrak, DL (2013) Procalcitonin-guided antibiotic therapy: A systematic review and meta-analysis. JOURNAL OF HOSPITAL MEDICINE 8(9): 530 - 540	- Systematic review used as source of primary studies
Uranga, Ane, Artaraz, Amaia, Bilbao, Amaia et al. (2020) Impact of reducing the duration of antibiotic treatment on the long-term prognosis of community acquired pneumonia. BMC pulmonary medicine 20(1): 261	- Study does not contain a relevant intervention *The study focuses on long term outcomes of short vs long antibiotic durations, and reports biomarker levels for a subsample of patients on day 5 and 30, but these biomarker levels are not used to inform decisions about antibiotic duration.*
Viasus, Diego, Del Rio-Pertuz, Gaspar, Simonetti, Antonella F et al. (2016) Biomarkers for predicting short-term mortality in community-acquired pneumonia: A systematic review and meta-analysis. The Journal of infection 72(3): 273-82	- Systematic review used as source of primary studies
Voiriot, Guillaume, Fartoukh, Muriel, Durand-Zaleski, Isabelle et al. (2021) Combined use of a broad-panel respiratory multiplex PCR and procalcitonin to reduce duration of antibiotics exposure in patients with severe community-acquired pneumonia (MULTI-CAP): a multicentre, parallel-group, open-label, individual randomised trial conducted in French intensive care units. BMJ open 11(8): e048187	- Study protocol only

PCT: procalcitonin; SR: systematic review

Prognostic studies

Study	Code [Reason]
Abu Elkhashab, A.E., Swelem, R.S., Abd Alla, A.E.D.A. et al. (2014) Etiological and prognostic values of procalcitonin in hospital-acquired pneumonia. Egyptian	- Data not reported in a format that could be extracted

Study	Code [Reason]
Journal of Chest Diseases and Tuberculosis 63(1): 201-206	
Akram, A R, Chalmers, J D, Taylor, J K et al. (2013) An evaluation of clinical stability criteria to predict hospital course in community-acquired pneumonia. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 19(12): 1174-80	- Data not reported in a format that could be extracted
Avci, Sema and Perincek, Gokhan (2020) The alveolar-arterial gradient, pneumonia severity scores and inflammatory markers to predict 30-day mortality in pneumonia. The American journal of emergency medicine 38(9): 1796-1801	- Data not reported in a format that could be extracted No means provided, only rank means from Mann-Whitney U test, so data not extractable
Aydemir, Semih and Hosgun, Derya (2022) Evaluation of the factors affecting long-term mortality in geriatric patients followed up in intensive care unit due to hospital-acquired pneumonia. Medicine 101(38): e30645	- Not a relevant study design Retrospective cohort study
Bloos F, Marshall JC, Dellinger RP et al. (2011) Multinational, observational study of procalcitonin in ICU patients with pneumonia requiring mechanical ventilation: a multicenter observational study. Critical care (London, England) 15(2): R88	- Study population excluded in protocol Included 175 patients requiring mechanical ventilation, 57 with community acquired pneumonia (CAP), 61 with ventilator associated pneumonia (VAP) and 57 with hospital acquired pneumonia (HAP). VAP is excluded from this review.
Boussekey N, Leroy O, Georges H et al. (2005) Diagnostic and prognostic values of admission procalcitonin levels in community-acquired pneumonia in an intensive care unit. Infection 33(4): 257-263	- Data not reported in a format that could be extracted Provides number of survivors by PCT thresholds rather than absolute values; cannot be used in meta-analysis
Boussekey, N Leroy, O Alfandari, S Devos, P Georges, H Guery, B (2006) Procalcitonin kinetics in the prognosis of severe community-acquired pneumonia. INTENSIVE CARE MEDICINE 32(3): 469 - 472	- Data not reported in a format that could be extracted Paper only reports median and IQR; no other usable data
Bruns, AH, Oosterheert, JJ, Hak, E et al. (2008) Usefulness of consecutive C-reactive protein measurements in follow-up of severe community-acquired pneumonia. The european respiratory journal 32(3): 726-732	- Study not reported in English
Cataudella, Emanuela, Giraffa, Chiara M, Di Marca, Salvatore et al. (2017) Neutrophil-	- Data not reported in a format that could be extracted

Study	Code [Reason]
To-Lymphocyte Ratio: An Emerging Marker Predicting Prognosis in Elderly Adults with Community-Acquired Pneumonia. Journal of the American Geriatrics Society 65(8): 1796-1801	Biomarker values only reported for overall sample, not by outcomes of interest
Dai, BQ; Yuan, XT; Liu, JM (2015) Value of serum procalcitonin for the guidance of antibiotic therapy in children with lower respiratory tract infection. Zhongguo dang dai er ke za zhi [Chinese journal of contemporary pediatrics] 17(12): 1292-1296	- Study not reported in English
Enersen, Christian Cosmus, Egelund, Gertrud Baunbaek, Petersen, Pelle Trier et al. (2023) The ratio of neutrophil-to-lymphocyte and platelet-to-lymphocyte and association with mortality in community-acquired pneumonia: a derivation-validation cohort study. Infection 51(5): 1339-1347	- Full text paper not available
Espana, Pedro P, Capelastegui, Alberto, Mar, Carmen et al. (2015) Performance of pro-adrenomedullin for identifying adverse outcomes in community-acquired pneumonia. The Journal of infection 70(5): 457-66	- Data not reported in a format that could be extracted All data of interest is reported as median and IQR, which cannot be extracted for meta-analysis
Farah, R Khamisy-Farah, R Makhoul, N (2018) Consecutive Measures of CRP Correlate with Length of Hospital Stay in Patients with Community-Acquired Pneumonia. ISRAEL MEDICAL ASSOCIATION JOURNAL 20(6): 345 - 348	- Data not reported in a format that could be extracted
Hong, Dae Young, Park, Sang O, Kim, Jong Won et al. (2016) Serum Procalcitonin: An Independent Predictor of Clinical Outcome in Health Care-Associated Pneumonia. Respiration; international review of thoracic diseases 92(4): 241-251	- Data not reported in a format that could be extracted Paper only reports median and IQR; no other usable data
Hong, Y.; Li, Y.; Xu, Z. (2020) Predictive value of GLI and CRP/albumin in patients with critical pneumonia. Acta Medica Mediterranea 36(3): 1957-1961	- Data not reported in a format that could be extracted
Ito, Akihiro, Ishida, Tadashi, Nakanishi, Yosuke et al. (2022) Inflammatory biomarkers are not useful for predicting prognosis in nursing and healthcare-associated pneumonia: A prospective, cohort study. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 28(5): 623-630	- Data not reported in a format that could be extracted Levels of biomarkers for survivors vs non-survivors are reported as median and IQR; cannot be extracted for meta-analysis. No other useable data reported

Study	Code [Reason]
Ito, Akihiro, Ito, Isao, Inoue, Daiki et al. (2020) The utility of serial procalcitonin measurements in addition to pneumonia severity scores in hospitalised community-acquired pneumonia: A multicentre, prospective study. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 92: 228-233	- Data not reported in a format that could be extracted Paper only reports median and IQR; no other usable data
Kasamatsu Y, Yamaguchi T, Kawaguchi T et al. (2012) Usefulness of a semi-quantitative procalcitonin test and the A-DROP Japanese prognostic scale for predicting mortality among adults hospitalized with community-acquired pneumonia. Respirology (Carlton, Vic.) 17(2): 330-336	- Data not reported in a format that could be extracted No comparisons reported for survivors vs non-survivors. Main analyses focus on use of the ADROP prognostic scale with biomarker together; cannot separate results just by biomarker.
Kaya, Y., Tas, N., Canakci, E. et al. (2018) Relationship of neutrophil-to-lymphocyte ratio with presence and severity of pneumonia. Journal of Clinical and Analytical Medicine 9(5): 452-457	- Data not reported in a format that could be extracted No information on duration of follow-up and only report 'mortality' - unclear whether 30-day mortality or longer.
Kim, Min Woo; Lim, Jee Yong; Oh, Sang Hoon (2017) Mortality prediction using serum biomarkers and various clinical risk scales in community-acquired pneumonia. Scandinavian journal of clinical and laboratory investigation 77(7): 486-492	- Not a relevant study design Retrospective review of medical records
Krüger S, Ewig S, Marre R et al. (2008) Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. The European respiratory journal 31(2): 349-355	- Data not reported in a format that could be extracted Median and IQR only; cannot be pooled for meta-analysis, no other useable outcome data reported
Li, Dan, Gu, Haiyan, Chen, Lei et al. (2023) Neutrophil-to-lymphocyte ratio as a predictor of poor outcomes of Mycoplasma pneumoniae pneumonia. Frontiers in immunology 14: 1302702	- Duplicate reference Included in review for CYP
Lindstrom, S T and Wong, E K C (2014) Procalcitonin, a valuable biomarker assisting clinical decision-making in the management of community-acquired pneumonia. Internal medicine journal 44(4): 390-7	- Not a relevant study design Study compares a group using PCT algorithm for switching from IV to oral antibiotics and compares it to a hypothetical control arm using hospital data. Not an included study type for this review. Data also not reported in a format that can be extracted
Liu, Xue-Hua, Li, Qing, Zhang, Pei et al. (2014) Serum mannose-binding lectin and	- Data not reported in a format that could be extracted

Study	Code [Reason]
C-reactive protein are potential biomarkers for patients with community-acquired pneumonia. Genetic testing and molecular biomarkers 18(9): 630-5	Study compares CRP levels of patients admitted with CAP vs patients admitted with other non-CAP illness. Where CRP levels for survivors vs non-survivors with CAP are reported, only p values provided - no means or SDs for extraction.
Malek, F., Gohari, A., Mirmohammadkhani, M. et al. (2019) Relationship between the serum level of C-reactive protein and severity and outcomes of community-acquired pneumonia. Archives of Clinical Infectious Diseases 14(2): e63893	- Data not reported in a format that could be extracted Only p values of key analyses reported; data on rates of outcome by group (e.g., survivors vs non-survivors) not reported so cannot be extracted.
Malezieux-Picard, Astrid, Nasce, Alberto, Azurmendi, Leire et al. (2022) Kinetics of inflammatory biomarkers to predict one-year mortality in older patients hospitalized for pneumonia: a multivariable analysis. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 122: 63-69	- Outcome to be predicted do not match that specified in the protocol Mortality only measured at 1-year follow up
Martin-Loeches, Ignacio, Valles, Xavier, Menendez, Rosario et al. (2014) Predicting treatment failure in patients with community acquired pneumonia: a case-control study. Respiratory research 15: 75	- Data not reported in a format that could be extracted AUC not included due to protocol deviation
McCluskey, Suzanne M, Schuetz, Philipp, Abers, Michael S et al. (2017) Serial Procalcitonin as a Predictor of Bacteremia and Need for Intensive Care Unit Care in Adults With Pneumonia, Including Those With Highest Severity: A Prospective Cohort Study. Open forum infectious diseases 4(1): ofw238	- Data not reported in a format that could be extracted Paper does not report absolute values, information for eligible outcomes is reported in figures with p values only so raw data cannot be extracted.
Menéndez, R Cavalcanti, M Reyes, S Mensa, J Martinez, R Marcos, MA Filella, X Niederman, M Torres, A (2008) Markers of treatment failure in hospitalised community acquired pneumonia. THORAX 63(5): 447 - 452	- Data not reported in a format that could be extracted Paper only reports median and IQR; no other usable data reported
Menéndez, R Martínez, R Reyes, S Mensa, J Filella, X Marcos, MA Martínez, A Esquinas, C Ramirez, P Torres, A (2009) Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia. THORAX 64(7): 587 - 591	- Data not reported in a format that could be extracted Paper reports medians and IQR only, which cannot be pooled for meta-analysis. No other useable data reported.
Pereira, Jose Manuel, Teixeira-Pinto, Armando, Basilio, Carla et al. (2013) Can we predict pneumococcal bacteremia in	- Outcome to be predicted do not match that specified in the protocol

Study	Code [Reason]
patients with severe community-acquired pneumonia?. Journal of critical care 28(6): 970-4	Outcome was development of bacteraemia - not an outcome listed in protocol
Peñafiel, FS Rossel, GS Oksenberg, KF Sánchez, AR Patiño, OD (2019) Immunocompetent adults hospitalized for a community-acquired pneumonia: Serum C-reactive protein as a prognostic marker. REVISTA MEDICA DE CHILE 147(8): 983 - 992	- Study not reported in English
Pieralli, F., Vannucchi, V., Silverii, M.V. et al. (2016) The real life application of a procalcitonin-based algorithm to reduce antibiotic exposure in hospitalized patients with Community acquired pneumonia: A proof of concept. Italian Journal of Medicine 10(3): 213-218	- Not a relevant study design Case control study, but decision over whether patient was assigned to case or control group was made by attending physician, and the two groups were not comparable at baseline (case group had admission PCT of 12.1; control group was 1.4, suggesting very significant differences in PCT levels before implementing algorithm).
Porfyridis, Ilias, Georgiadis, Georgios, Vogazianos, Paris et al. (2014) C-reactive protein, procalcitonin, clinical pulmonary infection score, and pneumonia severity scores in nursing home acquired pneumonia. Respiratory care 59(4): 574-81	- Study population excluded in protocol NHAP; 53% of sample had aspiration pneumonia
Self, Wesley H, Grijalva, Carlos G, Williams, Derek J et al. (2016) Procalcitonin as an Early Marker of the Need for Invasive Respiratory or Vasopressor Support in Adults With Community-Acquired Pneumonia. Chest 150(4): 819-828	- Data not reported in a format that could be extracted
Shi, Yan, Xu, Ying-chun, Rui, Xi et al. (2014) Procalcitonin kinetics and nosocomial pneumonia in older patients. Respiratory care 59(8): 1258-66	- Outcome to be predicted do not match that specified in the protocol Primary study outcome was 'clinical improvement vs no clinical improvement,' defined as symptom resolution vs symptom deterioration. This outcome is not listed in the protocol.
Subedi, Bibidh, Louzon, Patricia, Zappas, Kristie et al. (2020) Impact of Pharmacist-Led Procalcitonin-Guided Antibiotic Therapy in Critically Ill Patients With Pneumonia. Hospital pharmacy 55(3): 204-210	- Duplicate reference
Tamura, Masaki, Watanabe, Masato, Nakajima, Akira et al. (2014) Serial quantification of procalcitonin (PCT) predicts clinical outcome and prognosis in	- Data not reported in a format that could be extracted No biomarker values provided for key comparisons; only p value reported. Other

Study	Code [Reason]
patients with community-acquired pneumonia (CAP). Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 20(2): 97-103	comparisons provide results in diagrams or figures where absolute values are not provided. No data to extract.
Torres, Antoni, Cilloniz, Catia, Ferrer, Miquel et al. (2015) Bacteraemia and antibiotic-resistant pathogens in community acquired pneumonia: risk and prognosis. The European respiratory journal 45(5): 1353-63	- Outcome to be predicted do not match that specified in the protocol Primary study outcome was development of bacteraemia; not listed as an included primary outcome in protocol, none of the primary outcomes were reported so could not include if only one secondary outcome reported
Yin, Qin, Liu, Bo, Chen, Yunxia et al. (2014) Soluble thrombomodulin to evaluate the severity and outcome of community-acquired pneumonia. Inflammation 37(4): 1271-9	- Data not reported in a format that could be extracted Paper only reports median and IQR; no other usable data
Zheng, Nan; Zhu, Dongmei; Han, Yi (2020) Procalcitonin and C-reactive protein perform better than the neutrophil/lymphocyte count ratio in evaluating hospital acquired pneumonia. BMC pulmonary medicine 20(1): 166	- Not a relevant study design Retrospective cohort study
Zhu, W., Chen, P., Hu, L. et al. (2021) Serum levels of SIRT3 and other inflammatory factors are associated with clinical outcomes and prognosis in severe community-acquired pneumonia in adults: A prospective study. Medicine (United States) 100(32): e26721	- Data not reported in a format that could be extracted Paper only reports median and IQR; no other usable data
Zhydkov, Andriy, Christ-Crain, Mirjam, Thomann, Robert et al. (2015) Utility of procalcitonin, C-reactive protein and white blood cells alone and in combination for the prediction of clinical outcomes in community-acquired pneumonia. Clinical chemistry and laboratory medicine 53(4): 559-66	- Data not reported in a format that could be extracted Paper only reports median and IQR; no other usable data

J.2 Children

Study	Code [Reason]
Agnello, Luisa, Bellia, Chiara, Di Gangi, Maria et al. (2016) Utility of serum procalcitonin and C-reactive protein in	- Retrospective cohort study

Study	Code [Reason]
severity assessment of community-acquired pneumonia in children. Clinical biochemistry 49(12): 47-50	
Balanza, Nuria, Erice, Clara, Ngai, Michelle et al. (2023) Prognostic accuracy of biomarkers of immune and endothelial activation in Mozambican children hospitalized with pneumonia. PLOS global public health 3(2): e0001553	- Data not reported in an extractable format *No mean or median values of CRP reported - only significance of comparisons; all other data presented in figures where absolute values cannot be extracted.*
Barak-Corren, Yuval, Horovits, Yair, Erlichman, Matti et al. (2021) The prognostic value of C-reactive protein for children with pneumonia. Acta paediatrica (Oslo, Norway : 1992) 110(3): 970-976	- Retrospective cohort study
Bashir, Anam, Khan, Raheel, Thompson, Stephanie et al. (2022) A retrospective observational study of biomarker levels and severity assessment in pediatric community-acquired pneumonia. Medicine 101(32): e30010	- Retrospective cohort study
Benet, Thomas, Picot, Valentina Sanchez, Awasthi, Shally et al. (2017) Severity of Pneumonia in Under 5-Year-Old Children from Developing Countries: A Multicenter, Prospective, Observational Study. The American journal of tropical medicine and hygiene 97(1): 68-76	- Data not reported in an extractable format *Data reported by hypoxic vs non-hypoxic pneumonia, rather than for other outcomes of interest (e.g., survivors vs non-survivors). Also outcomes are reported as median and IQR.*
Berg, Are Stuwitz, Inchley, Christopher Stephen, Fjaerli, Hans Olav et al. (2020) Assessing Severity in Pediatric Pneumonia: Predictors of the Need for Major Medical Interventions. Pediatric emergency care 36(4): e208-e216	- Data not reported in an extractable format *Study only reports median and IQR, which cannot be extracted for meta-analysis. No other useable data reported*
Bhat, Javeed Iqbal, Charoo, Bashir A, Mukherjee, Aparna et al. (2021) Risk of Hospitalization in Under-five Children With Community-Acquired Pneumonia: A Multicentric Prospective Cohort Study. Indian pediatrics 58(11): 1019-1023	- Main study outcome does not match that specified in the protocol *Outcome is hospitalisation; outcomes of interest for the review are other markers of prognosis e.g., , need for invasive ventilation, or mortality.*
Bozkurt, H.B. (2021) Is there any relationship between C-reactive protein/albumin ratio and clinical severity of childhood community-acquired pneumonia. Turkish Journal of Biochemistry 46(6): 647-653	- Retrospective cohort study
Chen, Lumin, Miao, Chong, Chen, Yanling et al. (2021) Age-specific risk factors of	- Retrospective cohort study

Study	Code [Reason]
severe pneumonia among pediatric patients hospitalized with community-acquired pneumonia. Italian journal of pediatrics 47(1): 100	
Chu, Fu-Lu, Li, Chen, Liu, Yiqing et al. (2023) Peripheral blood parameters for predicting PICU admission and mechanical ventilation in pediatric inpatients with human parainfluenza virus-induced pneumonia. Journal of medical virology 95(4): e28752	- Retrospective cohort study
Dai, BQ; Yuan, XT; Liu, JM (2015) Value of serum procalcitonin for the guidance of antibiotic therapy in children with lower respiratory tract infection. Zhongguo dang dai er ke za zhi [Chinese journal of contemporary pediatrics] 17(12): 1292-1296	- Study not reported in English *Chinese*
Don, M., Valent, F., Korppi, M. et al. (2007) Efficacy of serum procalcitonin in evaluating severity of community-acquired pneumonia in childhood. Scandinavian Journal of Infectious Diseases 39(2): 129-137	- Main study outcome does not match that specified in the protocol *Focus of the paper is on using biomarkers to distinguish the bacterial or viral aetiology of CAP; no data reported for outcomes listed in protocol (e.g., , need for ventilation, mortality).*
Dudognon, D., Levy, C., Chalumeau, M. et al. (2021) Diagnostic Accuracy of Routinely Available Biomarkers to Predict Bacteremia in Children With Community-Acquired Pneumonia: A Secondary Analysis of the GPIP/ACTIV Pneumonia Study in France, 2009-2018. Frontiers in Pediatrics 9: 684628	- Main study outcome does not match that specified in the protocol *Study outcome was bacteraemia - not a primary outcome of interest for this review; only secondary outcome and no other primary outcomes reported in this paper*
Fernandes, Catarina D, Arriaga, Maria B, Costa, Maria Carolina M et al. (2019) Host Inflammatory Biomarkers of Disease Severity in Pediatric Community-Acquired Pneumonia: A Systematic Review and Meta-analysis. Open forum infectious diseases 6(12): ofz520	- Systematic review used as source of primary studies
Fonseca, T.S., Vasconcellos, A.G., Gendrel, D. et al. (2019) Recovery from childhood community-acquired pneumonia in a developing country: Prognostic value of serum procalcitonin. Clinica Chimica Acta 489: 212-218	- Main study outcome does not match that specified in the protocol *Comparisons are between children with pneumococcal and non-pneumococcal pneumonia; analyses are focused on admission PCTs levels in children who remained febrile after 48h vs those who didn't, this is not an outcome of interest.*
Giulia, B Luisa, A Concetta, S Bruna, LS Chiara, B Marcello, C (2015) Procalcitonin	- Systematic review used as source of primary studies

Study	Code [Reason]
and community-acquired pneumonia (CAP) in children. CLINICA CHIMICA ACTA 451: 215 - 218	
Han, L.; Feng, R.; Meng, J. (2018) Treatment of severe pediatric pneumonia by antibiotic de-escalation therapy. International Journal of Clinical and Experimental Medicine 11(3): 2610-2616	- Study does not contain a relevant intervention *Antibiotic de-escalation is not based on the use of biomarkers. Study reports on trial comparing IV then oral antibiotics with oral only. Biomarkers are measured at baseline and follow-up but do not inform antibiotic use.*
Kruger, Stefan, Ewig, Santiago, Kunde, Jan et al. (2010) Assessment of inflammatory markers in patients with community-acquired pneumonia--influence of antimicrobial pre-treatment: results from the German competence network CAPNETZ. Clinica chimica acta; international journal of clinical chemistry 411(2324): 1929-34	- Does not contain a population of children with pneumonia *Adult patients only. Not a relevant include for adults review of biomarkers either because this study is looking at the influence of pre-treatment with antibiotics on admission levels of biomarkers.*
Le Roux, David M, Nicol, Mark P, Vanker, Aneesa et al. (2021) Factors associated with serious outcomes of pneumonia among children in a birth cohort in South Africa. PloS one 16(8): e0255790	- Data not reported in an extractable format *Raw data not reported so could not be extracted for meta-analysis*
Li, Qiaoling, Zhang, Xueya, Chen, Bo et al. (2022) Early predictors of lung necrosis severity in children with community-acquired necrotizing pneumonia. Pediatric pulmonology 57(9): 2172-2179	- Does not contain a population of children with pneumonia *Population had already developed necrotizing pneumonia, study predicted severity thereafter.*
Lin, Chao-Jen, Chen, Po-Yen, Huang, Fang-Liang et al. (2006) Radiographic, clinical, and prognostic features of complicated and uncomplicated community-acquired lobar pneumonia in children. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi 39(6): 489-95	- Full text paper not available
Lu, Yan and Song, Lei (2023) Clinical Significance of Procalcitonin, Lactic Acid, and Endotoxin Testing for Children With Severe Pneumonia and Sepsis. Alternative therapies in health and medicine 29(3): 218-223	- Full text paper not available
Ma, Lu, Yan, Jingli, Song, Wenliang et al. (2023) Early peripheral blood lymphocyte subsets and cytokines in predicting the severity of influenza B virus pneumonia in	- Retrospective cohort study

Study	Code [Reason]
children. Frontiers in cellular and infection microbiology 13: 1173362	
Masarweh, Kamal, Gur, Michal, Toukan, Yazeed et al. (2021) Factors associated with complicated pneumonia in children. Pediatric pulmonology 56(8): 2700-2706	- Retrospective cohort study
McDonald, Chloe R, Leligdowicz, Aleksandra, Conroy, Andrea L et al. (2022) Immune and endothelial activation markers and risk stratification of childhood pneumonia in Uganda: A secondary analysis of a prospective cohort study. PLoS medicine 19(7): e1004057	- Data not reported in an extractable format *No data on comparisons of biomarker levels between those with and without outcomes of interest (e.g., survivors vs non-survivors). The only data reported for CRP and PCT are AUROC in supplementary analyses.*
Page, Anne-Laure, de Rekeneire, Nathalie, Sayadi, Sani et al. (2014) Diagnostic and prognostic value of procalcitonin and C-reactive protein in malnourished children. Pediatrics 133(2): e363-70	- Does not contain a population of children with pneumonia *Study population is infants hospitalised with severe acute malnutrition plus a medical complication. Only 56/311 patients were diagnosed with CAP and results are not reported separately for CAP patients.*
Qi, Xuejiao, Dong, Yihui, Lin, Xiaojie et al. (2021) Value of Neutrophil to Lymphocyte Ratio, Platelet to Lymphocyte Ratio, and Red Blood Cell Distribution Width in Evaluating the Prognosis of Children with Severe Pneumonia. Evidence-based complementary and alternative medicine : eCAM 2021: 1818469	- Retrospective cohort study
Sartori, Laura F, Zhu, Yuwei, Grijalva, Carlos G et al. (2021) Pneumonia Severity in Children: Utility of Procalcitonin in Risk Stratification. Hospital pediatrics 11(3): 215-222	- Data not reported in an extractable format *Stratified pneumonia severity into mild, moderate, severe and very severe; reported PCT levels in each severity group, but reported median and IQR only. No other usable outcome data*
Shan, Wei, Shi, Ting, Chen, Kaile et al. (2019) Risk Factors for Severe Community-aquired Pneumonia Among Children Hospitalized With CAP Younger Than 5 Years of Age. The Pediatric infectious disease journal 38(3): 224-229	- Retrospective cohort study
Sung, Myongsoon, Roh, Eui Jeong, Lee, Eun Sil et al. (2022) Assessment of variables associated with prolonged admission duration in children with Mycoplasma pneumoniae pneumonia. The clinical respiratory journal 16(11): 756-767	- Main study outcome does not match that specified in the protocol *Study focuses on various biomarker levels in patients with mycoplasma pneumoniae (MP); main analysis compares levels between MRMP (macrolide-resistant MP) and MSMP (macrolide-susceptible MP). No*

Study	Code [Reason]
	primary outcomes from protocol included in this study.
Taras, Roxana, Mahler, Beatrice, Balgradean, Mihaela et al. (2023) The Role of Mannose-Binding Lectin and Inflammatory Markers in Establishing the Course and Prognosis of Community-Acquired Pneumonia in Children. Children (Basel, Switzerland) 10(11)	- Retrospective cohort study
Tsai, Chih-Min, Tang, Kuo-Shu, Cheng, Ming-Chou et al. (2020) Use of saliva sample to detect C-reactive protein in children with pneumonia. Pediatric pulmonology 55(9): 2457-2462	- Main study outcome does not match that specified in the protocol *Focus of this study is on comparing salivary CRP levels with serum CRP levels taken from blood samples. Does not examine association between CRP levels and outcomes of interest.*
Tugcu, Gokcen Dilsa, Ozsezen, Beste, Turkyilmaz, Irem et al. (2022) Risk factors for complicated community-acquired pneumonia in children. Pediatrics international : official journal of the Japan Pediatric Society 64(1): e15386	- Retrospective cohort study
van de Maat, Josephine S, Peeters, Daphne, Nieboer, Daan et al. (2020) Evaluation of a clinical decision rule to guide antibiotic prescription in children with suspected lower respiratory tract infection in The Netherlands: A stepped-wedge cluster randomised trial. PLoS medicine 17(1): e1003034	- Does not contain a population of children with pneumonia *<50% of the sample had pneumonia. Intervention also focused on use of a risk assessment tool to reduce antibiotic use, rather than biomarkers alone (although CRP was part of the risk assessment tool)*
Williams, Derek J. Zhu, Yuwei Grijalva, Carlos G. Self, Wesley H. Harrell, Frank E., Jr. Reed, Carrie Stockmann, Chris Arnold, Sandra R. Ampofo, Krow K. Anderson, Evan J. Bramley, Anna M. Wunderink, Richard G. McCullers, Jonathan A. Pavia, Andrew T. Jain, Seema Edwards, Kathryn M. (2016) Predicting Severe Pneumonia Outcomes in Children. PEDIATRICS 138(4)	- Study does not contain a relevant intervention *Biomarkers were not assessed in this study*
Williams, Derek J, Hall, Matthew, Auger, Katherine A et al. (2015) Association of White Blood Cell Count and C-Reactive Protein with Outcomes in Children Hospitalized for Community-acquired Pneumonia. The Pediatric infectious disease journal 34(7): 792-3	- Retrospective cohort study
Wrotek, August; Wrotek, Oliwia; Jackowska, Teresa (2022) Low Levels of Procalcitonin	- Retrospective cohort study

Study	Code [Reason]
Are Related to Decreased Antibiotic Use in Children Hospitalized Due to Influenza. Diagnostics (Basel, Switzerland) 12(5)	
Wu, G.; Wu, S.; Wu, H. (2017) Comparison of Procalcitonin Guidance-Administered Antibiotics with Standard Guidelines on Antibiotic Therapy in Children with Lower Respiratory Tract Infections: A Retrospective Study in China. Medical Principles and Practice 26(4): 316-320	- Retrospective cohort study
Youssef, Ahmed S, Fanous, Mina, Siddiqui, Faisal J et al. (2020) Value of Blood Cultures in the Management of Children Hospitalized with Community-Acquired Pneumonia. Cureus 12(5): e8222	- Retrospective cohort study

AUROC: area under the receiver operating curve; CAP: community acquired pneumonia; CRP: C-reactive protein; IQR: interquartile range; IV: intravenous; PCT: procalcitonin

Economic studies

Study	Code [Reason]
Akyil, Fatma Tokgoz, Hazar, Armagan, Erdem, Ipek et al. (2015) Hospital Treatment Costs and Factors Affecting These Costs in Community-Acquired Pneumonia. Turkish thoracic journal 16(3): 107-113	- Study does not contain a relevant intervention *Costing study, does not compare interventions*
Andrews, Annie Lintzenich, Simpson, Annie N, Heine, Daniel et al. (2015) A Cost-Effectiveness Analysis of Obtaining Blood Cultures in Children Hospitalized for Community-Acquired Pneumonia. The Journal of pediatrics 167(6): 1280-6	- US study
Antunes, C, Pereira, M, Rodrigues, L et al. (2020) Hospitalization direct cost of adults with community-acquired pneumonia in Portugal from 2000 to 2009. Pulmonology 26(5): 264-267	- Study does not contain a relevant intervention *Costing study, does not compare interventions*
Asti, L, Bartsch, S M, Umscheid, C A et al. (2019) The potential economic value of sputum culture use in patients with community-acquired pneumonia and healthcare-associated pneumonia. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 25(8): 1038e1-1038e9	- US study
Buendia, Jefferson A and Patino, Diana Guerrero (2023) Corticosteroids for the treatment of respiratory infection by Mycoplasma pneumoniae in children: A cost-utility analysis. Pediatric pulmonology 58(10): 2809-2814	- Non OECD country *Columbia*
Cammarota, Gianmaria; Vetrugno, Luigi; Longhini, Federico (2023) Lung ultrasound monitoring: impact on economics and outcomes. Current opinion in anaesthesiology 36(2): 234-239	- Does not contain a population of people with only pneumonia, includes people with acute respiratory failure *Unclear if the patients are intubated* - US study *Unclear if the study is US or Europe* -Abstract only
Ceyhan, Mehmet, Ozsurekci, Yasemin, Aykac, Kubra et al. (2018) Economic burden of pneumococcal infections in children under 5 years of age. Human vaccines & immunotherapeutics 14(1): 106-110	- Study does not contain a relevant intervention *Non-comparative costing analysis*

Study	Code [Reason]
Cisco, Giulio, Meier, Armando N, Senn, Nicolas et al. (2024) Cost-effectiveness analysis of procalcitonin and lung ultrasonography guided antibiotic prescriptions in primary care. The European journal of health economics : HEPAC : health economics in prevention and care	- setting in primary care whereas the review was in secondary care
Costa, Nadege, Hoogendijk, Emiel O, Mounie, Michael et al. (2017) Additional Cost Because of Pneumonia in Nursing Home Residents: Results From the Incidence of Pneumonia and Related Consequences in Nursing Home Resident Study. Journal of the American Medical Directors Association 18(5): 453e7-453e12	- Study does not contain a relevant intervention *Non-comparative costing analysis*
Hyams, Catherine; Williams, O Martin; Williams, Philip (2020) Urinary antigen testing for pneumococcal pneumonia: is there evidence to make its use uncommon in clinical practice?. ERJ open research 6(1)	- Review article but not a systematic review, all primary studies were check for relevance
Ito, Akihiro, Ishida, Tadashi, Tokumasu, Hironobu et al. (2017) Impact of procalcitonin-guided therapy for hospitalized community-acquired pneumonia on reducing antibiotic consumption and costs in Japan. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 23(3): 142-147	- Not a relevant study design *Costing study not a cost utility study*
Javanbakht, Mehdi, Moradi-Lakeh, Maziar, Mashayekhi, Atefeh et al. (2022) Continuous Monitoring of Respiratory Rate with Wearable Sensor in Patients Admitted to Hospital with Pneumonia Compared with Intermittent Nurse-Led Monitoring in the United Kingdom: A Cost-Utility Analysis. PharmacoEconomics - open 6(1): 73-83	- Study does not contain a relevant intervention *Continuous monitoring versus intermittent monitoring, NEWS used in both arms*
Khole, Aalok V, Dionne, Emily, Zitek-Morrison, Emily et al. (2023) Cefepime extended infusion versus intermittent infusion: Clinical and cost evaluation. Antimicrobial stewardship & healthcare epidemiology : ASHE 3(1): e119	- US study
Latif, Marina, Guo, Ning, Tereshchenko, Larisa G et al. (2023) Association of hospital spending with care patterns and mortality in patients hospitalized with community-acquired pneumonia. Journal of hospital medicine 18(11): 986-993	- Study does not contain a relevant intervention *US costing study with no comparative interventions*

Study	Code [Reason]
Leem, Ah Young, Jung, Won Jai, Kang, Young Ae et al. (2014) Comparison of methicillin-resistant Staphylococcus aureus community-acquired and healthcare-associated pneumonia. Yonsei medical journal 55(4): 967-74	- Not a relevant study design *Not a health economic study*
Macaya, M.C.; Ridulfo, A.H.; Ramirez-Santana, M. (2015) Comparison of costs and health outcomes of users with community-acquired pneumonia treated at home or in traditional hospitalization: An exploratory study of 40 cases. Value in Health Regional Issues 8: 112-115	- Study not reported in English *Reported in Spanish*
McKinnell, James A, Corman, Shelby, Patel, Dipen et al. (2018) Effective Antimicrobial Stewardship Strategies for Cost-effective Utilization of Telavancin for the Treatment of Patients With Hospital-acquired Bacterial Pneumonia Caused by Staphylococcus aureus. Clinical therapeutics 40(3): 406-414e2	- Study does not contain a relevant intervention *US study that compares different antibiotics rather than length of treatments*
Meacock, Rachel, Sutton, Matt, Kristensen, Soren Rud et al. (2017) Using Survival Analysis to Improve Estimates of Life Year Gains in Policy Evaluations. Medical decision making : an international journal of the Society for Medical Decision Making 37(4): 415-426	- Study does not contain a relevant intervention *Modelling survival not cost effectiveness of treatment*
Miners, Lisa, Huntington, Susie, Lee, Nathaniel et al. (2023) An economic evaluation of two PCR-based respiratory panel assays for patients admitted to hospital with community-acquired pneumonia (CAP) in the UK, France and Spain. BMC pulmonary medicine 23(1): 220	- Not a relevant study design *Cost consequence study*
Patel, Archana B, Bang, Akash, Singh, Meenu et al. (2015) A randomized controlled trial of hospital versus home based therapy with oral amoxicillin for severe pneumonia in children aged 3 - 59 months: The IndiaCLEN Severe Pneumonia Oral Therapy (ISPOT) Study. BMC pediatrics 15: 186	- Non OECD country *India*
Pliakos, Elina Eleftheria, Andreatos, Nikolaos, Tansarli, Giannoula S et al. (2019) The Cost-Effectiveness of Corticosteroids for the Treatment of Community-Acquired Pneumonia. Chest 155(4): 787-794	- US study

Study	Code [Reason]
Prasath, T.M., Ramachandran, V., Geetha, S. et al. (2019) Hidden Markov model-based cough sound analysis for classification of asthma and pneumonia in pediatric. Drug Invention Today 11(7): 1692-1695	- Full text paper not available
Przybilla, Jens, Ahnert, Peter, Bogatsch, Holger et al. (2020) Markov State Modelling of Disease Courses and Mortality Risks of Patients with Community-Acquired Pneumonia. Journal of clinical medicine 9(2)	- Study does not contain a relevant intervention *Does not include costs*
Reynolds, Courtney A, Finkelstein, Jonathan A, Ray, G Thomas et al. (2014) Attributable healthcare utilization and cost of pneumonia due to drug-resistant streptococcus pneumonia: a cost analysis. Antimicrobial resistance and infection control 3: 16	- Study does not contain a relevant intervention *Looking at different antibiotics not the length of the courses*
Rozenbaum, Mark H, Mangen, Marie-Josee J, Huijts, Susanne M et al. (2015) Incidence, direct costs and duration of hospitalization of patients hospitalized with community acquired pneumonia: A nationwide retrospective claims database analysis. Vaccine 33(28): 3193-9	- Study does not contain a relevant intervention *Costing analysis without comparators*
Shi, Honghao, Guo, Wanjie, Zhu, He et al. (2019) Cost-Effectiveness Analysis of Xiyanping Injection (Andrographolide Sulfonate) for Treatment of Adult Community Acquired Pneumonia: A Retrospective, Propensity Score-Matched Cohort Study. Evidence-based complementary and alternative medicine : eCAM 2019: 4510591	- Study does not contain a relevant intervention *Andrographolide Sulfonate injection*
Shiri, Tinevimbo, Khan, Kamran, Keaney, Katherine et al. (2019) Pneumococcal Disease: A Systematic Review of Health Utilities, Resource Use, Costs, and Economic Evaluations of Interventions. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 22(11): 1329-1344	- Study does not contain a relevant intervention *Vaccines and antibiotics (not length of treatment)*
Sultana, Marufa, Sarker, Abdur Razzaque, Ali, Nausad et al. (2019) Economic evaluation of community acquired pneumonia management strategies: A	- Study does not contain a relevant intervention *Different antibiotics in adults and bubble continuous positive airway pressure in newborns*

Study	Code [Reason]
systematic review of literature. PloS one 14(10): e0224170	
Tesfaye, Solomon H, Loha, Eskindir, Johansson, Kjell Arne et al. (2022) Cost-effectiveness of pulse oximetry and integrated management of childhood illness for diagnosing severe pneumonia. PLOS global public health 2(7): e0000757	- Non OECD country *Ethiopia*
Torres, Antoni, Bassetti, Matteo, Welte, Tobias et al. (2020) Economic analysis of ceftaroline fosamil for treating community-acquired pneumonia in Spain. Journal of medical economics 23(2): 148-155	- Study does not contain a relevant intervention *Different antibiotics not different durations*
Wagner, A P, Enne, V I, Livermore, D M et al. (2020) Review of health economic models exploring and evaluating treatment and management of hospital-acquired pneumonia and ventilator-associated pneumonia. The Journal of hospital infection 106(4): 745-756	- Study does not contain a relevant intervention *Different antibiotics not different durations*
Xie, Xuanqian; Sinclair, Alison; Dendukuri, Nandini (2017) Evaluating the accuracy and economic value of a new test in the absence of a perfect reference test. Research synthesis methods 8(3): 321-332	Included in review question 4.2
Zhang, Shanshan, Sammon, Peter M, King, Isobel et al. (2016) Cost of management of severe pneumonia in young children: systematic analysis. Journal of global health 6(1): 010408	- Study does not contain a relevant intervention *Costing study with no outcomes*