National Clinical Guideline Centre

Research recommendations

Pneumonia

Diagnosis and management of community- and hospital-acquired pneumonia in adults

Clinical guideline 191

Appendix M

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Contents

1 Research recommendations

1.1 Research question: Urine antigen testing

1. In moderate- to high-severity community-acquired pneumonia does using legionella and pneumococcal urinary antigen testing in addition to other routine tests improve outcomes?

Why this is important

Current practice and evidence suggests that giving a combination of antibiotics to patients with moderate- to high- severity community-acquired pneumonia reduces mortality. However no randomised controlled trial has looked at using simple urinary antigen testing to target treatment and therefore allow for better antibiotic stewardship, increase compliance and potentially reduce costs.

PICO question	**Population: patients with moderate- to high-severity CAP** **Intervention: urinary pneumococcal and Legionella antigen testing in addition to blood and sputum cultures** **Comparison: blood and sputum culture alone** **Outcomes:** • antibiotics used • mortality • speed of recovery • re-admission • complications • drug tolerability.
Importance to patients or the population	The use of urinary antigen tests is not established because of the lack of evidence of cost effectiveness and because their use has not yet been proven to change outcomes. The urine legionella test targets serogroup 1 and although this is the most common serotype responsible for at least 90% of all cases, it is still possible to miss non-serogroup 1 cases. While the specificity of both tests is very good, the sensitivity will be in the mid- to upper 70s. The antigen tests are estimated to cover 40—50% of all pathogens responsible for pneumonia (and the majority of CAP cases), so potentially their use could lead to a switch from empirical dual therapy to a targeted single antibiotic. The use of combination antibiotics is based on the need to effectively cover the most significant pathogens responsible for CAP. Where the pathogen is clearly defined, there is no evidence that combination therapy provides a better outcome in terms of mortality, length of hospital stay or adverse events when compared to monotherapy. Broad-spectrum antibiotic therapy is known to promote the emergence of drug resistance which can potentially limit drug options to costly agents, with fewer oral options and increased risk of adverse events such as *Clostridium difficile* infection. The availability of these tests might enable effective monotherapy with narrow-spectrum antibiotic therapy which will support initiatives encouraging judicious antibiotic use and in the long-term slow the emergence of antibiotic resistance. Currently there is no accepted method of estimating a cost for the advantage of antibiotic stewardship but the continuing availability of lower-cost antibiotics and intravenous to oral options

	strengthens the case for cost effectiveness.
Relevance to NICE guidance	The current recommendation for urinary antigen testing is weak. Further data would help facilitate a clearer recommendation.
Relevance to the NHS	Identifying pathogens is costly. Establishing the most cost-effective microbiological investigations would benefit patients and the NHS alike.
National priorities	Pneumonia represents a high burden of illness to the NHS and high-severity pneumonia has a high mortality rate.
Current evidence base	Current practice within the UK comprises use of beta-lactam antibiotics together with a macrolide for moderate- to high-severity pneumonias. No RCT was found to compare those agents to a beta-lactamase or other narrow-spectrum antibiotic therapy (section 9.1). Urinary antigen testing should help identify the responsible organism and allow targeted treatment with reduced mortality and decreased inappropriate use of antibiotics. There are 2 randomised studies looking at antigen tests for CAP. Both had outcomes other than just mortality. The Falguera study looked at the role of empiric compared with targeted treatment for CAP using a combination of urine pneumococcal and Legionella antigen tests. Both arms were treated empirically and only randomised when clinically stable. In addition to mortality, the study looked at relapse, re-admission, length of stay, ITU admission and duration of antibiotic therapy. The Van der Eerden study used a combination of invasive and non-invasive tests including blood, sputum/BAL and pleural fluid cultures in addition to antigen tests and reported mortality, length of stay and quality-of-life. Both studies showed serious bias and indirectness (excluded patient population, employed non-routine tests and demonstrated differences in randomisation parameters).
Equality	This research recommendation does not address an equality issue.
Study design	Randomised controlled trial.
Feasibility	The availability of tests and prevalence of pneumonia makes this trial highly feasible.
Importance	High. Unless new evidence is gained, no accurate assessment of cost effectiveness will be possible, and no clear recommendation relating to the utility of the antigen tests can be formulated in future updates.

1.2 C-reactive protein guided antibiotic duration

2. In patients hospitalised with moderate- to high-severity community-acquired pneumonia, does using C-reactive protein monitoring in addition to clinical observation to guide antibiotic duration safely reduce the total duration of antibiotic therapy compared with a fixed empirical antibiotic course?

Why this is important

The recommended duration of antibiotic therapy for adults hospitalised with moderate- to high-severity community-acquired pneumonia is based on evidence of very low quality; no relevant clinical trials were identified by NICE. The burden of community-acquired pneumonia is large, and its treatment accounts for a high proportion of antibiotic use in hospitals. Overuse of antibiotics is associated with antimicrobial resistance, which is a national and global priority.

PICO question	**Population: Patients (adults) hospitalised with moderate- to high- severity CAP receiving treatment with 7 to 10 days of antibiotic therapy (according to NICE guidelines).**
	Intervention: CRP monitoring at fixed time points such as day 1, 3, 5 and 7 in addition to clinical observation.
	Comparison: Clinical observation.
	Outcomes:
	• primary outcome
	  ○ duration of antibiotic therapy
	• secondary outcomes measured at 28 days from hospital admission:
	  ○ 'clinical cure'
	  ○ pneumonia complications (development of empyema requiring a chest drain, ITU admission, development of lung abscess)
	  ○ mortality
	  ○ hospital re-admission
	  ○ total volume of antibiotic used.

Importance to patients or the population	Shorter courses of antibiotic therapy would be associated with lower volumes of antibiotic use with expected reductions in adverse effects for patients, reductions in healthcare resource utilisation, including length of hospital stay, and wider downstream effects related to antimicrobial resistance.
Relevance to NICE guidance	The answer to this question would generate new evidence to enable a clear recommendation regarding the optimal duration of antibiotic therapy.
Relevance to the NHS	If found to be cost effective, this intervention would offer a financial advantage. In addition, benefits relating to the development of antimicrobial resistance would be accrued; these benefits are less easily measurable but are recognised to be of high importance.
National priorities	The question is relevant to the UK 5-year Antimicrobial Resistance Strategy published in September 2013.
Current evidence base	No clinical trials were identified by NICE to inform questions related to a) the duration of antibiotic therapy in moderate- and high-severity CAP and b) the use of CRP monitoring strategies to determine when to stop antibiotic therapy. The available evidence is summarised in Sections 9.9 and 12 of the NICE Pneumonia Clinical Guideline. There is trial evidence that CRP monitoring can safely inform antibiotic prescribing decisions in patients presenting in primary care with lower respiratory tract infections. Data from observational cohort studies indicate that for

	hospitalised patients with CAP who are on antibiotic therapy, CRP levels measured at days 3 to 4 following admission are associated with prognosis.
Equality	This research recommendation does not address an equality issue.
Study design	Blinded randomised controlled trial.
Feasibility	A trial is feasible. There are no ethical or technical issues.
Other comments	Different approaches to the use of CRP to direct antibiotic duration may be considered. However, approaches that require daily measurements of CRP are less likely to be acceptable to patients and less likely to be cost effective. Measurement of CRP at fixed points may be preferable.
Importance	High. This research is essential. Unless new evidence is gained, no clear recommendation relating to the duration of antibiotic therapy can be formulated in future updates.

1.3 Continuous positive pressure ventilation

3. What is the clinical effectiveness of continuous positive pressure ventilation compared with usual care in patients with community-acquired pneumonia and type I respiratory failure without a history of chronic obstructive pulmonary disease?

Why this is important

Type I respiratory failure is a common feature of pneumonia. Mild type I respiratory failure is easily corrected with low levels of supplemental oxygen, whereas severe life-threatening hypoxemia needs immediate intubation and invasive ventilation. Research into whether continuous positive pressure ventilation improves gas exchange and subsequent outcomes, such as mortality, could help improve care for patients with respiratory failure between these extremes.

PICO question	**Population: Adults treated in hospital for community-acquired pneumonia, with type I respiratory failure, without co-existent COPD, who do not require immediate intubation.** **Intervention: Use of CPAP in addition to usual care.** **Comparison: Usual medical treatment, including supplemental oxygen and antibiotics.** **Outcomes:** • mortality at 30 days • need for intubation and invasive ventilation; • length of stay (in critical care, and total hospital stay) • clinical cure • quality-of-life • complications (of pneumonia, CPAP, and subsequent intubation and ventilation if required) • changes in PaO2:FiO2 ratio with time.
Importance to patients or the population	Whilst some patients find CPAP unpleasant, the majority are able to tolerate it well. Any reduction in mortality, length of stay, need for invasive ventilation or associated complications would be of benefit to patients.
Relevance to NICE guidance	The GDG did not feel a specific recommendation in favour or against CPAP could be made as part of the current guidance due to the lack of evidence. CPAP is occasionally used in these circumstances in current clinical practice. A suitable study on CPAP in CAP would influence future recommendations.
Relevance to the NHS	If CPAP were found to be clinically effective for this indication, then benefits to the NHS could include reduced mortality, length of stay, requirement for ITU admissions and complications in patients with pneumonia. If CPAP were found to be safe and clinically effective then it could potentially be applied to less sick patients outside the ITU setting, as has happened with non-invasive ventilation in exacerbations of COPD. This would yield cost savings in terms of monitoring and ITU bed days if such patients no longer required ITU admission. CPAP does usually require a higher level of care than routine ward-based care which could have cost-implications, but these would likely be outweighed by reductions in bed days at level 3 (Intensive Care).
National priorities	N/A
Current evidence base	Only 2 relevant randomised controlled trials on this topic were identified, only 1 of which reported the majority of the most important outcomes. The numbers included in the studies were small and imprecision was seen around many of the results providing no conclusive evidence on which to build a recommendation.
Equality	Patients with COPD should be excluded, as the benefits of non-invasive ventilation during acute exacerbations are now well-established, with clear

	guidance on when to use this treatment. Patients with a ceiling of care (for example, in those for whom a decision not to escalate to invasive ventilation has been made, or with a "do not attempt resuscitation" order) would not necessarily have to be excluded as CPAP could have beneficial effects in this group, but would have to be analysed as a distinct subgroup.
Study design	Prospective randomised controlled trial.
Feasibility	Similar studies have been conducted in the COPD population examining the use of non-invasive ventilation, which suggests that such a study should be feasible. Community-acquired pneumonia is relatively common, so recruitment of an adequate number of patients should be possible, especially if the study was conducted in multiple centres. The proportion of patients with pneumonia that would be included would depend on the inclusion criteria for the severity of type I respiratory failure. Satisfactory criteria might include patients with a respiratory rate < 30 requiring oxygen at FiO_2 of ≥ 0.35 but less than 0.6 to maintain a pO_2 of > 8kPa, or with a PaO_2/FiO_2 ratio between 12 and 25.
Other comments	None.
Importance	High. This is currently a controversial area, with the potential to have a significant impact on outcomes.

1.4 Hospital-acquired pneumonia

4. Can rapid microbiological diagnosis of hospital-acquired pneumonia reduce the use of extended-spectrum antibiotic therapy, without adversely affecting outcomes?

Why this is important:

Data are limited on the microbiology of hospital-acquired pneumonia to guide antibiotic therapy. Hospital-acquired infections can be caused by highly resistant pathogens that need treatment with extended-spectrum antibiotic therapy (for example extended-spectrum penicillins, third-generation cephalosporins, aminoglycosides, carbapenems, linezolid, vancomycin, or teicoplanin), as recommended by British Society of Antimicrobial Chemotherapy guidance. Because routine microbial tests lack sensitivity and take 24-48 hours to identify a causative pathogen, patient characteristics are used to guide antibiotic choice. However, this may lead to unnecessary use of extended-spectrum antibiotics in patients infected with non-resistant organisms, and inappropriate use of first-line antibiotic therapy (such as beta-lactam stable penicillins, macrolides or doxycycline) in patients infected with resistant organisms.

Rapid diagnostic tests to identify causative bacterial pathogens and whether they are resistant to antibiotics may have a role in guiding antibiotic choice for post-operative hospital-acquired pneumonia.

To limit population variability and include high-risk patients spending time in intensive care, studies should include postoperative patients from different surgical specialties.

PICO question	**Population: Adult (> 18 years, no upper age limit necessary) male and female inpatients with post-operative hospital-acquired pneumonia (HAP); that is, pneumonia developing as a complication of a hospital admission for gastroenterological, vascular, gynaecological and orthopaedic surgery. The trial will exclude severely immunocompromised patients, or patients developing ventilator-acquired pneumonia (VAP). It will include patients who develop HAP on the ward and then require ITU care, with or without mechanical ventilation.** **Intervention: Antibiotic choice guided by rapid microbiological testing to identify the potential causative pathogen and their antibiotic resistance patterns (use of a similar test to the GeneExpert PCR cassette now used in cases of suspected TB).** **Comparator: Conventional management of HAP (empirical antibiotic choice guided by division of patients into 'simple' or 'complex' HAP according to existing British Society for Antimicrobial Chemotherapy guidelines).** **Outcomes: Between treatment groups the outcomes might be:** • Potential primary outcomes: ○ total use of extended-spectrum antibiotics (extended-spectrum penicillins, third-generation cephalosporins, aminoglycosides, carbapenems, linezolid, vancomycin, or teicoplanin) ○ total use of all antibiotics ○ patient outcome (in-patient and 30-day mortality, total length of hospital stay, time to clinical stability from diagnosis of HAP) • Potential secondary outcomes: ○ time to microbial diagnosis ○ proportion of patients with a defined microbial aetiology of HAP ○ resistance patterns of causative bacterial pathogens in HAP ○ concordance of positive rapid and conventional microbial tests ○ length of stay in intensive care ○ proportion of patients admitted to intensive care

Importance to patients or the population	If the trial identifies a more effective antibiotic strategy for treatment of HAP, the importance for patients is potentially large. Patient-centred benefits that might be identified by the trial include for patients with HAP: • reduced length of hospital admission, morbidity and mortality due to more appropriate antibiotic therapy for HAP • a higher proportion of patients receiving more acceptable/easy treatment options for HAP (namely an oral rather than an intravenous antibiotic) • reduced chance of secondary hospital-acquired infections due to antibiotic use (*C. difficile*) or intravenous catheters (cellulitis, septicaemia) • reductions in the spread of antibiotic-resistant organisms within hospital and therefore future infection with resistant and difficult-to-treat bacteria that are associated with a high mortality.
Relevance to NICE guidance	Due to the lack of evidence the NICE guidelines committee was unable to make any recommendation of antibiotic treatment for HAP; a trial in this area would therefore be highly informative and is very likely to lead eventually to a modification of NICE guidelines.
Relevance to the NHS	If the trial shows that rapid microbial diagnosis and identification of antibiotic resistance reduces use of extended spectrum antibiotics there could be major financial advantages by reducing excess costs due to • unnecessary use of expensive antibiotics • avoiding prolonged length of stay for treatment of HAP using intravenous rather than oral antibiotics • decreased incidence of secondary hospital-acquired infections • more indirectly, but important in the long term, help limit the spread of bacteria resistant to second/third-line antibiotics. If the trial is negative then that will also be helpful as it will • help reduce the use of rapid diagnostic microbiological testing into an area where it is of little benefit (and help control costs) • will provide data on HAP for planning future trials, which are at present inhibited by the almost complete lack of high-quality data in this area.
National priorities	This research question is directly relevant to at least two national NHS priorities: • prevention/effective treatment of nosocomial infections (both HAP itself and secondary infections caused by the treatment of HAP) • Reducing the spread of antibiotic-resistant bacterial pathogens.
Current evidence base	The current research base is very limited – the NICE guidelines committee researchers identified a total of 6 RCTs of empirical antibiotic therapy for HAP, comparing varied antibiotic regimens. All the evidence was low or very low quality according to GRADE criteria, and none addressed the specific question this trial will address. Overall there was insufficient evidence for any specific recommendations for empirical antibiotic treatment of HAP by the NICE guidelines committee.
Equality	Not specifically relevant.
Study design	Randomised controlled trial in post-operative patients developing HAP. Due to the nature of the intervention (rapid microbial testing), the clinicians caring for the patients cannot be blinded to intervention arm.
Feasibility	HAP is very common and an acute disease, so recruiting adequate numbers of patients for a trial over a relatively short period is very feasible. Specific technical issues are as follows: Choice of rapid diagnostic test for use in HAP – a suitable test would provide an answer within a few hours, cover a large range of potential causative Gram positive and Gram negative bacterial pathogens, and also identify antibiotic resistance. Tests fulfilling these criteria are becoming available, but data on whether there is any variation in the efficacy of the different existing options or

	which test might be most appropriate for patients with HAP are lacking. The rapid diagnostic test would have to be available to multiple wards at each study site presenting some logistical difficulties. A single protocol for choosing empirical and pathogen-specific treatment options will have to be adopted across all participating sites.
Other comments	To our knowledge, this question has not been addressed in any previous studies and will not be addressed in the near future by an already funded study.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline