National Clinical Guideline Centre

Pneumonia

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

Clinical guideline <…>

Appendix C

June 2014

Draft for consultation

Commissioned by the National Institute for Health and Care Excellence

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Funding
National Institute for Health and Care Excellence

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1 Diagnostic tests for patients with lower respiratory tract infection in the community

Component	Description
Review question	In adults with lower respiratory tract infection in the community, what is the clinical value and cost effectiveness of testing C-reactive protein, procalcitonin or performing a chest X-ray over clinical assessment to inform antibiotic prescribing decisions and need for hospital admission?
Objectives	The aim of this review is to determine the predictive ability of CRP, PCT and CXR for guiding clinical decision-making regarding which patients presenting with LRTI require an antibiotic or should be referred to hospital.
Population	Adults with LRTI presenting in the community who have had clinical assessment • Adult is defined as aged 18 years or over.
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • those patients with suspected pneumonia compared to those without suspected pneumonia • older people (age > 75 years) compared with younger people.
Comparative strategies	Antibiotic therapy or hospital admission guided by: • C-reactive protein (CRP) • Procalcitonin (PCT) • chest X-ray (positive) • standard assessments.
Outcomes	• Hospital admission. • Antibiotic treatment. • Mortality. • Re-consultation. • Health-related quality-of-life. • Resolution of symptoms/treatment failure (opposite direction).
Importance of outcomes	Critical outcomes: • hospital admission • antibiotic treatment.
Study design	Systematic reviews of RCTs and RCTs. The GDG members advised that that they were not aware of any RCT data directly comparing PCT and CRP. Therefore, it was decided that observational studies will be considered if there is no RCT evidence for the comparison of PCT and CRP to provide supplementary information regarding the ability of PCT and CRP to identify patients with pneumonia and guide antibiotic treatment and hospital admission.
Population size and directness	No restrictions.
Setting	• Primary care. • Community settings in which NHS care is received.
Search Strategy	See appendix
Review Strategy	**Appraisal of methodological quality** • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data** • Meta-analysis will be conducted where appropriate.

Notes	• Results are needed for HE model. • There is not yet an established threshold for CRP and PCT measurements to guide antibiotic therapy. Therefore, threshold definitions will be tested according to study protocols – but differences will be noted in the interpretation of results. • We will consider point of care testing only – sequential testing is not considered practical in the community.

2 Severity assessment

2.1 Tools for assessing disease severity in people with lower respiratory tract infection in the community

Component	Description
Review question	In adults presenting with a lower respiratory tract infection or suspected community-acquired pneumonia in the community, what is the most accurate and cost-effective severity assessment tool to identify patients whose outcome will be improved by referral to hospital?
Objectives	The aim of this review is to establish the prognostic accuracy of various severity assessment tools for determining which people with LRTI presenting in the community would benefit from referral to hospital.
Population	Adults with LRTI presenting in the community (at first presentation) • Adult is defined as aged 18 years or over.
Index test: Severity assessment tools/clinical markers	• CRB65. • SIRS criteria. • NICE LRTI suggested tool. • MEWS – modified early warning score. • Biomarkers (CRP and PCT). • Individual markers (for example, heart rate, blood pressure, respiratory rate) – only if compared with a severity assessment tool.
Reference standard or target condition/patient outcomes	Patient outcomes: • mortality • hospital admission • health-related quality-of-life (measured by CAP symptom questionnaire, EQ5D or SF-36). Other outcomes: • test practicality.
Subgroups and sensitivity analyses	The following groups will be assessed separately: • suspected pneumonia or pneumonia not suspected. Important confounders: • age • comorbidities (previous heart, lung and liver disease) • malignancies.
Outcomes	If thresholds are established/pre-defined: • relative risk (RR) or odds ratio (OR) (and ultimately risk difference) for patient outcomes listed above for those in higher or lower risk groups • area under the curve (AUC) (through ROC analysis). Supplementary information only if no other data (RRs, ORs, AUCs) available through: • sensitivity • specificity • positive predictive value (PPV) • negative predictive value (NPV).
Study design	• Systematic reviews (SRs), RCTs and non-RCTs comparative study including any of the above severity tools. • External validation studies.

	• Case-control studies and internal validation studies will be excluded.
Population size and directness	• At least 10 events per covariate (for accurate multivariate analysis to be possible). • Studies with indirect populations will not be considered.
Setting	• Primary care. • Community settings in which NHS care is received.
Search Strategy	See appendix Key study from MM
Review Strategy	**Appraisal of methodological quality** • The methodological quality of each study will be assessed using NICE checklists. **Synthesis of data:** • Meta-analysis will not be conducted. • Priority will be given to results as presented by AUCs (discriminatory analysis) and results of multivariate analysis (OR or RRs (95% CI). • When the studies report the raw data of outcome of interest by low/intermediate/high risk groups as defined by tools, this information will be summarized in RRs and corresponding absolute effect measures.
Notes/additional information	Only tools that are externally validated will be assessed. As non-RCTs studies are prone to publication bias, results from the largest studies will be highlighted. As some of the tools have already incorporated some of the confounding factors, results from the univariate analysis will be equally presented. Test practicality will also be considered by the GDG in deciding which tool is 'best'.

2.2 Tools for assessing disease severity in people with community-acquired pneumonia at first presentation to Accident & Emergency

Component	Description
Review question	In adults with community-acquired pneumonia (presenting to Accident & Emergency) what is the most accurate and cost-effective severity assessment tool to stratify patients at first presentation according to who would benefit from • hospital admission? • ITU assessment?
Objectives	The aim of this review is to establish the prognostic accuracy of various severity assessment tools for determining which people with pneumonia should be admitted to hospital or ITU.
Population	Adults diagnosed with community-acquired pneumonia at first presentation/at point of diagnosis. • Adult is defined as aged 18 years or over. • Pneumonia diagnosis made on the basis of chest X-ray for those in a hospital setting. • CAP is defined as pneumonia that is acquired outside hospital.
Index test: Severity assessment tools	• CURB65 (high risk group as ≥ 3). • CRB65 (high risk group as ≥ 2). • PSI (high risk group as ≥ IV). • American Thoracic Society (ATS) 2001 criteria. • Infectious Disease Society of America/ATS (IDSA/ATS).

	- Major criteria. - Minor criteria. • SMART-COP (high risk ≥ 3). • Early warning score (EWS). • SCAP score. • SIRS criteria. • SCCM/ACCP organ dysfunction criteria. • Sepsis severity score. • CORB. • APACHEII. • SOFA – Sepsis-Related/Sequential Organ Failure Assessment Score. • CDIS – clinician determined illness severity. • A-DROP. • eCURB.
Reference standard or target condition/patient outcomes	Patient outcomes: • mortality – as an indicator of when hospital or ITU admission is required • hospital admission • assessment for ITU admission (accept ITU admission or need for invasive ventilation or vasopressor support as surrogates). Other outcomes: • test practicality.
Subgroups and sensitivity analyses	The following groups will be assessed separately: • suspected pneumonia or pneumonia not suspected. Important confounders: • age • comorbidities (previous heart, lung and liver disease) • malignancies.
Outcomes	Established thresholds for PSI, CURB65, CURB, CRB65 and SMART-COP (from validation studies) will be used: • relative risk or odds ratio will be calculated for different risk groups • area under the curve (AUC) (through ROC analysis). Supplementary information only if no other data (RRs, ORs, AUCs) available through: • sensitivity • specificity • positive predictive value (PPV) • negative predictive value (NPV).
Study design	• Systematic reviews, RCTs and non-RCTs comparative study including any of the above severity tools.
Population size and directness	• At least 10 events per covariate (for accurate multivariate analysis to be possible). • Studies with indirect populations will not be considered.
Setting	• Secondary care. • Tertiary care. • Community settings in which NHS care is received.
Search Strategy	See appendix
Review Strategy	**Appraisal of methodological quality** • The methodological quality of each study will be assessed using NICE checklists.

	Synthesis of data • Meta-analysis will not be conducted. When frequencies of outcomes are reported by risk group in each severity tool, data will be summarized in absolute effect (from pooled estimate of effect size). The relative effect (RR) will be presented by the median study and the range of RRs of included studies. • Priority will be given to results as presented by AUCs (discriminatory analysis) and results of multivariate analysis (OR or RRs (95% CI).
Notes/additional information	As non-RCTs studies are very prone to publication bias, results from the largest studies will be highlighted. As some of the tools have already incorporated some of the confounding factors, results from the univariate analysis will be equally presented. We will only include studies looking at a population diagnosed with pneumonia at first presentation. The criteria cannot be applied until diagnosis is made and severity assessment throughout the remainder of the illness after the point of presentation/diagnosis is not included in this review. Note whether studies looking at ITU admission exclude patients whose level of care is limited (for example by DNR order) and analyse separately.

2.3 Tools for determining disease severity in patients with hospital-acquired pneumonia

Component	Description
Review question	In adults with hospital-acquired pneumonia what is the most accurate and cost-effective severity assessment tool to stratify patients at first presentation according to who would benefit from ITU assessment?
Objectives	The aim of this review is to establish the prognostic accuracy of various severity assessment tools for determining which people with HAP should be admitted to ITU.
Population	Adults diagnosed with hospital-acquired pneumonia at first presentation/at point of diagnosis: • adult is defined as aged 18 years or over • pneumonia diagnosis made on the basis of chest X-ray • HAP is defined as pneumonia that occurs 48 hours or more after hospital admission and is not incubating at hospital admission.
Index test: Severity assessment tools	• Any identified tools.
Reference standard or target condition/patient outcomes	Patient outcomes: • mortality • assessment for ITU admission (accept ITU admission or need for invasive ventilation or vasopressor support as surrogates). Other outcomes: • test practicality.
Subgroups and sensitivity analyses	The following groups will be assessed separately: • studies including or excluding patients whose level of care is limited (for example by DNR order). Important confounders: • age • comorbidities (previous heart, lung and liver disease)

	• malignancies.
Outcomes	If thresholds are established/pre-defined: • relative risk (RR) or odds ratio (OR) (and ultimately risk difference) for patient outcomes listed above for those in higher compared with lower risk groups • area under the curve (AUC) (through ROC analysis). Supplementary information only if no other data (RRs, ORs, AUCs) available through: • sensitivity • specificity • positive predictive value (PPV) • negative predictive value (NPV).
Study design	• Systematic reviews, RCTs and non RCTs comparative study including any of the above severity tools. • External validation studies. • Case-control studies and internal validation studies will be excluded.
Population size and directness	• At least 10 events per covariate (for accurate multivariate analysis to be possible). • Studies with indirect populations will not be considered.
Setting	• Secondary care. • Tertiary care.
Search Strategy	See appendix
Review Strategy	**Appraisal of methodological quality** • The methodological quality of each study will be assessed using NICE checklists. **Synthesis of data** • Meta-analysis will not be conducted. • Priority will be given to results as presented by AUCs (discriminatory analysis) and results of multivariate analysis (OR or RRs [95% CI]). • When the studies report the raw data of outcome of interest by low/high risk groups as defined by tools, this information will be summarized in RRs and corresponding absolute effect measures.
Notes/additional information	As non-RCTs studies are very prone to publication bias, results from the largest studies will be highlighted. As some of the tools have already incorporated some of the confounding factors, results from the univariate analysis will be equally presented. Only include studies looking at a population diagnosed with pneumonia at first presentation. The criteria cannot be applied until diagnosis is made and severity assessment throughout the remainder of the illness after the point of presentation/diagnosis is not included in this review.

3 Microbiological tests for patients with community-acquired pneumonia or hospital-acquired pneumonia

Component	Description
Review question	In adults with community-acquired pneumonia or hospital-acquired pneumonia in a hospital setting, what microbiological test or combination of tests at presentation (including urinary pneumococcal and urinary legionella antigen, blood culture and sputum culture) is most likely to be clinically and cost effective?
Objectives	The aim of this review is to determine whether targeted treatment is worthwhile (as opposed to empiric therapy) and, if so, what test is the most likely to be of value in hospital. • Targeted therapy is defined as using an antibiotic with as narrow an antimicrobial spectrum as possible which is active against a bacterium that is identified as being the likely causative organism. • Empirical therapy is considered to be antibiotic therapy likely to be active against the most likely causative bacteria in the absence of a definite known cause in that case.
Population	Adults diagnosed with pneumonia (community- or hospital-acquired): • adult is defined as aged 18 years or over • pneumonia diagnosis made on the basis of chest X-ray for those in a hospital setting • CAP is defined as pneumonia that is acquired outside hospital. • HAP is defined as pneumonia that occurs 48 hours or more after hospital admission and is not incubating at hospital admission. The review will be stratified by severity status as defined by formal severity assessment tools (such as PSI, CURB65, ATS) if available: • low-severity CAP • moderate- and high-severity CAP.
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • with or without antibiotic therapy prior to admission • timing of microbiological tests.
Intervention	Initial empiric treatment followed by targeted (pathogen-directed) antibiotic treatment strategies.
Index tests	Any of the following alone or in combination: • blood culture • sputum culture • urinary pneumococcal antigen • urinary legionella antigen. Invasive sampling techniques (e.g. bronchoalveolar lavage and protected brush sampling) will not be considered as they are only applicable to a small proportion of the population.
Comparison	Empirical (broad-spectrum) antibiotic treatment strategies without index tests OR Comparison between any of the index tests.
Outcomes	• Change in antibiotic prescription/treatment.

	• Length of stay. • Hospital re-admission. • Mortality (< 60 days). • Clinical cure (at end of follow-up). • Failure to respond to treatment (measured as clinical failure, clinical relapse or clinical instability). • Health-related quality-of-life (at 30 or 90 days). • Withdrawal due to adverse events. • Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS).
Importance of outcomes	**Critical outcomes for patient:** • mortality (< 60 days) • health-related quality-of-life. • length of stay.
Study design	Systematic reviews, comparative RCTs and non-randomised studies or cohorts with multivariate analysis • Unit of randomisation: individual patient or hospital cluster.
Population size and directness	• No restrictions on sample size. • Studies with indirect populations will not be considered.
Setting	• Secondary or tertiary care.
Search Strategy	See appendix
Review Strategy	**Appraisal of methodological quality** • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data** • Meta-analysis will be conducted where appropriate. • Data on all antibiotics will be pooled (empiric compared with targeted). • Default MIDs will be used: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes. • For continuous data final and change scores will be pooled and if any study reports both, the method used in the majority of studies will be analysed. **Hierarchy of evidence** • Comparative test-and-treat randomised studies of targeted treatment following test results compared with empirical treatment (no test) will be sought first. • Multivariable analyses from comparative observational studies will be sought, at a second stage, comparing outcomes among those with and without tests at point of entry will also be included. • If insufficient data from the above, non-comparative data will be explored to establish a range of values for the proportion of those tested with positive tests results and treatment changes (studies only reporting proportion positive and not how often treatment was altered will not be included at this stage).
Notes	Results are needed for HE model. We will record proportion with positive result too for HE model. We will not include studies that only report the proportion of tests that gave a positive result – these studies need to link the test results with change in management. *Do not automatically exclude studies that use one of the listed tests in addition to another test*

4 Antibiotic therapy

4.1 Timing of antibiotics for patients with community-acquired pneumonia

Component	Description
Review question	In adults with suspected community-acquired pneumonia is earlier rather than later antibiotic administration more clinically and cost effective?
Objectives	The aim of this review is to determine the impact of delay in antibiotic treatment in adults with suspected community-acquired pneumonia in all settings.
Population	Adults diagnosed with community-acquired pneumonia: • adult is defined as aged 18 years or over • pneumonia diagnosis made on the basis of chest X-ray for those in a hospital setting or based on clinical features in the community • CAP is defined as pneumonia that is acquired outside hospital. The review will be stratified by severity status as defined by formal severity assessment tools (such as PSI, CURB65, ATS): • low-severity CAP • moderate- and high-severity CAP. Note: Place of management will be used as a surrogate of severity assessment and each study will be assessed for directness of its population. Patients with CAP managed outside hospital or as outpatients will be considered as having low-severity CAP. Patients with CAP managed in hospital/ITU will be considered as having high-severity CAP. . Studies with ≥ 50% of their population assessed as low-severity CAP based on the severity assessment tools will be reviewed within the low-severity CAP stratum even if they are all managed in hospital. Studies with mixed CAP/nursing home pneumonia populations will be included if CAP ≥ 75% of the sample. Studies with mixed LRTI populations will be included if results are stratified for CAP or if CAP ≥ 75% of the sample. Studies that split the population into suspected (for example, pneumococcal and non-pneumococcal) origin will be included as long as treatment is not delayed to determine aetiology. Studies limited to “typical” pathogens only (proven or suspected) will be included if clearly stated that ≤ 30% excluded based on suspicion of atypical pathogens. Studies with mixed HAP/CAP populations will be excluded unless ≥ 75% are CAP. Studies will be excluded if exclusively assessing aspiration pneumonia.
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • intravenous and oral administration

	• duration of treatment (< 7 days or ≥ 7 days) • predominant disease aetiology (including resistance profiles) • CAP in primary care with diagnosis based on CXR or clinical assessment alone.
Intervention	**Immediate initiation of antibiotics** **Note**: only UK-licensed interventions and standard dose ranges will be considered.
Comparison	**Delayed initiation of antibiotics** • The agents used must be chosen according to the same criteria as in the intervention group.
Outcomes	• Mortality (at 30 days). • Hospital admission. • Length of hospital stay. • Clinical cure– success or improvement, clinical instability (opposite direction) will be accepted as surrogates. • Health-related quality-of-life (measured by CAP symptom questionnaire, EQ5D or SF-36) • Hospital re-admission. **Adverse events with wider healthcare implications:** • *C. difficile*-associated diarrhoea. **Adverse events relevant at the patient level:** • withdrawal due to treatment-related adverse events • complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS).
Importance of outcomes	**Critical outcomes:** • mortality • clinical cure • withdrawal due to treatment-related adverse events.
Study design	Systematic reviews and RCTs. • Unit of randomisation: individual patient or hospital cluster. If no RCTs are found, multivariable observational studies and comparative observational studies (including retrospective) which investigate the prognostic role of timing of administration of antibiotics on the outcomes will be considered. The GDG considered the following most important confounders: • age • comorbidities (previous heart, lung and liver disease) • malignancies.
Population size and directness	• No restrictions on sample size. • Treatment duration and dose within standard range (7 to 10 days or according to SPC or BNF). • Studies with indirect populations will not be considered.
Setting	• Primary care. • Secondary care.
Search Strategy	See appendix
Review Strategy	**Appraisal of methodological quality** • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data** • Meta-analysis will be conducted where appropriate.

	• The relationship between length of delay and outcome will also be examined. • Where appropriate, data on all antibiotics will be pooled, as long as they are chosen according to a pre-defined protocol. • For observational data, a summary of effects reported across studies will be included. If confounded factors differ between studies, then an individual relative effect (RR or OR) will be presented. • Default MIDs will be used: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes. • For continuous data final and change scores will be pooled and if any study reports both, the method used in the majority of studies will be analysed.
Notes	Note all individual adverse event frequencies in case needed for health economic model. Studies of specific pathogen outbreaks will be excluded (beyond the scope).

4.2 Timing of antibiotic therapy for patients with hospital-acquired pneumonia

Component	Description
Review question	In adults with hospital-acquired pneumonia is earlier rather than later antibiotic administration more clinically and cost effective?
Objectives	The aim of this review is to determine the impact of delay in antibiotic treatment in adults with suspected community-acquired pneumonia in all settings.
Population	Adults diagnosed with HAP: • adult is defined as aged 18 years or over • pneumonia diagnosis made on the basis of chest X-ray for those in a hospital setting • HAP is defined as pneumonia that occurs 48 hours or more after hospital admission and is not incubating at hospital admission (inclusion criterion). Note: • Both early and late onset HAP will be included. • Studies with mixed HAP/CAP populations will be excluded unless ≥ 75% are HAP. • Studies will be excluded if exclusively assessing aspiration pneumonia.
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • intravenous and oral administration • duration of treatment (< 7 days or ≥ 7 days) • predominant disease aetiology (including resistance profiles).
Intervention	**Immediate initiation of antibiotic therapy** **Note**: only UK-licensed interventions and standard dose ranges will be considered unless indicated by the GDG due to limited evidence regarding HAP population.
Comparison	**Delayed initiation of antibiotic therapy** • The agents used must be chosen according to the same criteria as in the intervention group.
Outcomes	• Mortality (at 30 days). • Hospital admission. • Length of hospital stay. • Clinical cure– success or improvement, clinical instability (opposite direction) will

	be accepted as surrogates. • Health-related quality-of-life (measured by CAP symptom questionnaire, EQ5D or SF-36). • Hospital re-admission. **Adverse events with wider healthcare implications:** • *C. difficile*-associated diarrhoea. **Adverse events relevant at the patient level:** • withdrawal due to treatment-related adverse events • complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS).
Importance of outcomes	**Critical outcomes:** • mortality • clinical cure • withdrawal due to treatment-related adverse events.
Study design	Systematic reviews and RCTs. • Unit of randomisation: individual patient or hospital cluster. If no RCTs are found, multivariable observational studies and comparative observational studies (including retrospective) which investigate the prognostic role of timing of administration of antibiotics on the outcomes will be considered.
Population size and directness	• No restrictions on sample size. • Treatment duration and dose within standard range (7 to 10 days or according to SPC or BNF). • Studies with indirect populations will not be considered.
Setting	• Secondary care. • Tertiary care.
Search Strategy	See appendix
Review Strategy	**Appraisal of methodological quality** • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data** • Meta-analysis will be conducted where appropriate. • **The relationship between length of delay and outcome will also be examined.** • Where appropriate, data on all antibiotics will be pooled, as long as they are chosen according to a pre-defined protocol. • For observational data, a summary of effects reported across studies will be included. If confounded factors differ between studies, then an individual relative effect (RR or OR) will be presented. • Default MIDs will be used: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes. • For continuous data final and change scores will be pooled and if any study reports both, the method used in the majority of studies will be analysed.
Notes	Note all individual adverse event frequencies in case needed for health economic model. Studies of specific pathogen outbreaks will be excluded (beyond the scope).

4.3 Empirical antibiotic choice for patients with community-acquired pneumonia

Component	Description
Review question	In adults with community-acquired pneumonia what is the most clinically- and cost-effective empirical antibiotic choice?
Objectives	The aim of this review is to determine which class/classes of empirical antibiotic therapy is/are optimal in terms of clinical and cost effectiveness as well as safety in adults with CAP. The classification of antibiotic therapy used in this guideline is available in Appendix N.
Population	Adults diagnosed with community-acquired pneumonia: • adult is defined as aged 18 years or over • pneumonia diagnosis made on the basis of chest X-ray for those in a hospital setting or based on clinical features in the community • CAP is defined as pneumonia that is acquired outside hospital. The review will be stratified by severity status as defined by formal severity assessment tools (such as PSI, CURB65, ATS): • low-severity CAP • moderate- and high-severity CAP • place of management will be used as a surrogate of formal severity assessment and each study will be assessed to determine the directness of the population. Patients with CAP managed outside hospital or as outpatients will be considered as having low-severity CAP. Patients with CAP managed in hospital/ITU will be considered as having high-severity CAP. . Note: Studies with ≥ 50% of their population assessed as low-severity CAP based on severity assessment tools will be reviewed in the low-severity CAP stratum even if patients are all managed in hospital. Studies with mixed CAP/nursing home pneumonia populations will be included if CAP constitutes ≥ 75% of the sample. Studies with mixed LRTI populations will be included if results are stratified for CAP or if CAP constitutes ≥ 75% of the sample. Studies that split the population into suspected (for example pneumococcal and non-pneumococcal) origin will be included as long as treatment is not delayed to determine aetiology. Studies limited to “typical” pathogens only (proven or suspected) will be included if clearly stated that ≤ 30% excluded based on suspicion of atypical pathogens. Studies with mixed HAP/CAP populations will be excluded unless ≥ 75% are CAP. Studies will be excluded if exclusively assessing aspiration pneumonia.
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • intravenous and oral administration • duration of treatment (< 7 days or ≥ 7 days) • predominant disease aetiology (including resistance profiles)

	• CAP in primary care with diagnosis based on CXR or clinical assessment alone.
Intervention	**Antibiotic monotherapy or dual therapy (with 2 agents from different classes) as first-line treatment for CAP:** • macrolides (including ketolides) • beta-lactams, subdivided into: o narrow-spectrum beta-lactams: – class 1: penicillin G (benzylpenicillin), phenoxymethylpenicillin (penicillin V) – class 2: ampicillin, amoxicillin o broad-spectrum beta-lactams: – beta-lactamase stable penicillins: co-amoxiclav, piperacillin-tazobactam, timentin (ticarcillin-clavulanic acid), flucloxacillin, co-fluampicil – cephalosporins • tetracyclines • fluoroquinolones, subdivided into: o non-respiratory: ciprofloxacin and ofloxacin o respiratory: levofloxacin and moxifloxacin **Route of administration** may be IV or oral, and studies that allow sequential therapy (intravenous switched to oral) in both arms will also be included. **Note**: only UK-licensed interventions and standard dose ranges will be considered.
Comparison	**The antibiotics listed in the intervention group (other than the one tested as intervention (monotherapy or dual therapy).** Studies comparing interventions within the same class will not be included except azithromycin compared with other macrolides (due to the different pharmacokinetic profile of azithromycin compared with other macrolides - it has a long tissue half-life).
Outcomes	• Mortality at 30 days. • Hospital admission (including ITU admission). • Length of hospital stay. • Clinical cure– success or improvement or maintaining clinical cure will be accepted as surrogates. • Health-related quality-of-life (measured by CAP symptom questionnaire, EQ5D or SF-36). **Adverse events with wider healthcare implications:** • *C. difficile*-associated diarrhoea. **Adverse events relevant at the patient level:** • withdrawal due to treatment-related adverse events • complications (composite of empyema, effusion, abscess, metastatic infection, MODS).
Importance of outcomes	**Critical outcomes:** • mortality • clinical cure • withdrawal due to treatment-related adverse events.
Study design	Systematic reviews of RCTs and RCTs. • Unit of randomisation: individual patient or hospital cluster. For the comparison of beta-lactams with beta-lactams together with macrolides (which is a widely-used first-line combination of treatment for CAP in UK clinical practice), the

	GDG noted that there may be lack of evidence from randomised trials; therefore, the GDG considered that observational studies (only with multivariate analyses) would also be appropriate to answer the review question.
Population size and directness	• No restrictions on sample size. • Treatment duration and dose within standard range (7 to 10 days or according to SPC or BNF). • Studies with patients who have previously received antibiotics will be considered as indirect evidence.
Setting	• Primary care. • Secondary care. • Community settings in which NHS care is received.
Search Strategy	See appendix
Review Strategy	**Appraisal of methodological quality** • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data** • Meta-analysis will be conducted where appropriate. • Data on all antibiotics within a class will be pooled, as defined above. • Only head-to-head studies will be included. • Default MIDs will be used: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes. • For continuous data final and change scores will be pooled and if any study reports both, the method used in the majority of studies will be analysed. • Studies will be downgraded for indirectness if included patients are treated in hospital and diagnosis not confirmed by CXR. • Studies will be downgraded for indirectness if excluding the elderly or limiting to the elderly.
Notes	Note all individual adverse event frequencies in case needed for health economic model. Studies assessing aminoglycosides, glycopeptides or sulphonamides will be excluded for CAP. Studies with the following types of populations will not be downgraded for indirectness (as the GDG considered it unlikely to influence the relative effectiveness of antibiotic treatment): • including young people (12 to 18 years) • high prevalence of uncommon pathogens (because this result may be due to the tests used being particularly sensitive to those pathogens) • excluding patients who are not eligible for penicillin • including patients with “prior antibiotic treatment” (as this review question focuses on empirical treatment).

4.4 Empirical antibiotic choice for patients with hospital-acquired pneumonia

Component	Description
Review question	In adults with hospital-acquired pneumonia what is the most clinically- and cost-effective empirical antibiotic choice?
Objectives	The aim of this review is to determine which class of empirical antibiotic therapy is optimal in terms of clinical and cost effectiveness as well as safety for adults with HAP.
Population	Adults diagnosed with HAP: • adult is defined as aged 18 years or over • pneumonia diagnosis made on the basis of chest X-ray for those in a hospital setting • HAP is defined as pneumonia that occurs 48 hours or more after hospital admission and is not incubating at hospital admission (inclusion criterion). Note: • Both early and late onset HAP will be included. • Studies with mixed HAP/CAP populations will be excluded unless ≥ 75% are HAP. • Studies will be excluded if exclusively assessing aspiration pneumonia.
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • intravenous and oral administration • duration of treatment (< 7 days or ≥ 7 days) • predominant disease aetiology (including resistance profiles).

Intervention	Antibiotic monotherapy or dual therapy (with two agents from different classes) as first-line treatment for HAP:
	• macrolides (including ketolides)
	• beta-lactams, subdivided into:
	  o narrow-spectrum beta-lactams:
	  – class 1: penicillin G (benzylpenicillin), phenoxymethylpenicillin (penicillin V)
	  – class 2: ampicillin, amoxicillin
	  o broad-spectrum beta-lactams:
	  – beta-lactamase stable penicillins: co-amoxiclav, piperacillin-tazobactam, timentin (ticarcillin-clavulanic acid), flucloxacillin, co-fluampicil
	  – cephalosporins
	  – carbapenems
	• tetracyclines
	• fluoroquinolones (all)
	• aminoglycosides
	• glycopeptides
	• sulphonamides
	
	Route of administration may be intravenous or oral, and studies that allow sequential therapy (IV switched to oral) in both arms will also be included.
	
	Note: only UK-licensed interventions and standard dose ranges will be considered unless indicated by the GDG due to limited evidence regarding HAP population.

Comparison	**Another class of antibiotics (single or dual) listed in the intervention group (other**

	than the one tested as intervention). Studies using a combination of *2 agents within the same class* will not be included.
Outcomes	• Mortality (at 30 days). • Hospital re-admission. • Length of hospital stay. • Clinical cure (at end of treatment) – success or improvement will be accepted as surrogates. **Adverse events with wider healthcare implications:** • *C. difficile*-associated diarrhoea. **Adverse events relevant at the patient level:** • withdrawal due to treatment-related adverse events • complications (composite of empyema, effusion, abscess, metastatic infection, MODS).
Importance of outcomes	Critical outcomes: • mortality • clinical cure • withdrawal due to treatment-related adverse events.
Study design	**RCTs or systematic reviews of RCTs** • Unit of randomisation: individual patient or hospital cluster.
Population size and directness	• No restrictions on sample size. • Treatment duration and dose within standard range (7 to 10 days or according to SPC or BNF). • Studies with patients who have previously received antibiotics will be considered as indirect evidence.
Setting	• Secondary care. • Tertiary care.
Search Strategy	See appendix
Review Strategy	**Appraisal of methodological quality** • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data** • Meta-analysis will be conducted where appropriate. • Data on all antibiotics within a class will be pooled, as defined above. • Only head-to-head studies will be included. • Default MIDs will be used: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes. • For continuous data final and change scores will be pooled and if any study reports both, the method used in the majority of studies will be analysed.
Notes	Note all individual adverse event frequencies in case needed for health economic model.

4.5 Duration of antibiotics for patients with community-acquired pneumonia

Component	Description
Review question	In adults with community-acquired pneumonia what is the clinical and cost effectiveness of short- compared with longer-course antibiotics?
Objectives	The aim of this review is to determine the optimal duration of antibiotic treatment in terms of clinical and cost-effectiveness as well as safety for adults with CAP.
Population	Adults diagnosed with community-acquired pneumonia: • adult is defined as aged 18 years or over • pneumonia diagnosis made on the basis of chest X-ray for those in a hospital setting or based on clinical features in the community • CAP is defined as pneumonia that is acquired outside hospital. The review will be stratified by severity status as defined by formal severity assessment tools (such as PSI, CURB65, ATS): • low-severity CAP • moderate- and high-severity CAP Note: Place of management will be used as a surrogate of severity assessment and each study will be assessed for directness of the population. Patients with CAP managed outside hospital or as outpatients will be considered as having low-severity CAP. Patients with CAP managed in hospital/ITU will be considered as having high-severity CAP. . Studies with ≥ 50% of population assessed as low-severity CAP based on the severity assessment tools will be reviewed within the low-severity stratum even if patients are all managed in hospital. Studies with mixed CAP/nursing home pneumonia populations will be included if CAP ≥ 75% of the sample. Studies with mixed LRTI populations will be included if results are stratified for CAP or if CAP ≥ 75% of the sample. Studies that split the population into suspected (for example pneumococcal and non-pneumococcal) origin will be included as long as treatment is not delayed to determine aetiology. Studies limited to “typical” pathogens only (proven or suspected) will be included if clearly stated that ≤ 30% excluded based on suspicion of atypical pathogens. Studies with mixed HAP/CAP populations will be excluded unless ≥ 75% are CAP. Studies will be excluded if exclusively assessing aspiration pneumonia.
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • intravenous and oral administration • predominant disease aetiology (including resistance profiles) • CAP in primary care with diagnosis based on CXR or clinical assessment alone.
Intervention	**Shorter duration of treatment** **Antibiotic treatment for CAP – any of the below alone or in combination:**

	• macrolides (including ketolides)
	• beta-lactams (cephalosporins and penicillins), subdivided into:
	  o narrow-spectrum beta-lactams:
	  – class 1: penicillin G (benzylpenicillin), phenoxymethylpenicillin (penicillin V)
	  – class 2: ampicillin, amoxicillin
	  o broad-spectrum beta-lactams:
	  – beta-lactamase stable penicillins: co-amoxiclav, piperacillin-tazobactam, timentin (ticarcillin-clavulanic acid), flucloxacillin, co-fluampicil
	  – cephalosporins
	• tetracyclines
	• respiratory fluoroquinolones.
	
	Route of administration may be intravenous or oral.
	Note: only UK-licensed interventions and standard dose ranges will be considered.

Comparison	**Longer duration of treatment** • Any agent from the above classes compared for different durations (i.e. different durations of **the same** antibiotic or different antibiotics **within a class**). Note: studies that switch from intravenous to oral will be included and the duration of interest will be the full treatment duration (intravenous + oral).
Outcomes	• Mortality (any point in time). • Relapse rate. • Hospital admission. • Length of hospital stay. • Clinical cure (at end of follow-up) – success or improvement will be accepted as surrogates. • Health-related quality-of-life (measured by CAP symptom questionnaire, EQ5D or SF-36). **Adverse events with wider healthcare implications:** • *C. difficile*-associated diarrhoea. **Adverse events relevant at the patient level:** • withdrawal due to treatment-related adverse events • complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS) • hospital re-admission.
Importance of outcomes	**Critical outcomes:** • mortality any point in time • clinical cure at the end of follow up • withdrawal due to treatment-related adverse events.
Study design	Systematic reviews of RCTs and RCTs • Unit of randomisation: individual patient or hospital cluster.
Population size and directness	• No restrictions on sample size. • Studies with indirect populations will not be considered.
Setting	• Primary care. • Secondary care. • Community settings in which NHS care is received.
Search Strategy	See appendix
Review Strategy	**Appraisal of methodological quality**

	• The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data** • Meta-analysis will be conducted where appropriate. • Results will be presented by pooling data on all antibiotics within a class. • Default MIDs will be used: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes. • For continuous data final and change scores will be pooled and if any study reports both, the method used in the majority of studies will be analysed.
Notes	Note all individual AE frequencies in case needed for HE model. Studies using biomarkers to allow targeted shortening of treatment will **not** be considered. Studies assessing aminoglycosides, glycopeptides or sulphonamides will be excluded for CAP.

4.6 Duration of antibiotics for patients with HAP

Component	Description
Review question	In adults with hospital-acquired pneumonia what is the clinical and cost effectiveness of short- compared with longer-course antibiotics?
Objectives	The aim of this review is to determine the optimal duration of antibiotic treatment in terms of clinical and cost-effectiveness as well as safety for adults with HAP.
Population	Adults diagnosed with HAP: • adult is defined as aged 18 years or over • pneumonia diagnosis made on the basis of chest X-ray for those in a hospital setting • HAP is defined as pneumonia that occurs 48 hours or more after hospital admission and is not incubating at hospital admission (inclusion criterion). Note: • Both early and late onset HAP will be included. • Studies with mixed HAP/CAP populations will be excluded unless ≥ 75% are HAP • Studies will be excluded if exclusively assessing aspiration pneumonia.
Subgroups	The following factors will be considered for subgroup analysis if heterogeneity is present: • Intravenous and oral administration • predominant disease aetiology (including resistance profiles).
Intervention	**Shorter duration of treatment** Antibiotic monotherapy or dual therapy (with two agents from different classes) as treatment for HAP: • macrolides (including ketolides) • beta-lactams, subdivided into: o narrow-spectrum beta-lactams: – class 1: penicillin G (benzylpenicillin), phenoxymethylpenicillin (penicillin V) – class 2: ampicillin, amoxicillin o broad-spectrum beta-lactams: – beta-lactamase stable penicillins: co-amoxiclav, piperacillin-tazobactam,

	timentin (ticarcillin-clavulanic acid), flucloxacillin, co-fluampicil – cephalosporins – carbapenems • tetracyclines • fluoroquinolones (all) • aminoglycosides • glycopeptides • sulphonamides **Route of administration** may be intravenous or oral, and studies that allow sequential therapy (intravenous switched to oral) in both arms will also be included. **Note**: only UK-licensed interventions and standard dose ranges will be considered unless indicated by the GDG due to limited evidence regarding HAP population.
Comparison	**Longer duration of treatment** • Any agent from the above classes compared for different durations (i.e. different durations of **the same** antibiotic or different antibiotics **within a class**). Note: studies that switch from intravenous to oral will be included and the duration of interest will be the full treatment duration (intravenous + oral).
Outcomes	• Mortality (any point in time). • Relapse rate. • Hospital re-admission. • Length of hospital stay. • Clinical cure– success or improvement will be accepted as surrogates. **Adverse events with wider healthcare implications:** • *C. difficile*-associated diarrhoea. **Adverse events relevant at the patient level:** • withdrawal due to treatment-related adverse events • complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS).
Importance of outcomes	• Mortality (at any point in time). • Clinical cure. • Withdrawal due to treatment-related adverse events.
Study design	**RCTs or systematic reviews of RCTs** • Unit of randomisation: individual patient or hospital cluster.
Population size and directness	• No restrictions on sample size. • Studies with indirect populations will not be considered.
Setting	• Secondary care. • Tertiary care.
Search Strategy	See appendix
Review Strategy	**Appraisal of methodological quality** • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data** • Meta-analysis will be conducted where appropriate. • Results will be presented by pooling data on all antibiotics within a class. • Default MIDs will be used: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes.

	• For continuous data final and change scores will be pooled and if any study reports both, the method used in the majority of studies will be analysed.
Notes	Note all individual AE frequencies in case needed for HE model. Studies using biomarkers to allow targeted shortening of treatment will **not** be considered.

5 Glucocorticosteroid treatment for patients with community-acquired pneumonia or hospital-acquired pneumonia

Component	Description
Review question	In adults with community-acquired pneumonia or hospital-acquired pneumonia requiring management in hospital, what is the clinical effectiveness and cost effectiveness of initial glucocorticosteroid treatment in addition to antibiotic treatment compared with antibiotic treatment alone?
Objectives	The aim of this review is to determine the clinical and cost-effectiveness as well as safety of antibiotic therapy alone compared with antibiotics plus glucocorticosteroid treatment for use in people with pneumonia requiring management in hospital.
Population	Adults diagnosed with pneumonia (hospital- or community-acquired) requiring management in hospital: • adult is defined as aged 18 years or over • pneumonia diagnosis made on the basis of chest X-ray for those in a hospital setting • CAP is defined as pneumonia that is acquired outside hospital • HAP is defined as pneumonia that occurs 48 hours or more after hospital admission and is not incubating at hospital admission (inclusion criterion). Studies with mixed HAP/CAP or HAP/VAP populations will be excluded, as will studies exclusively assessing aspiration pneumonia.
Subgroups	The following groups will be considered separately if data are available: • low compared with moderate or high severity The following factors will be considered for subgroup analysis if heterogeneity is present: • setting (hospital, ITU) • intravenous and oral administration. • antibiotic selection concordant with guidelines or non-concordant • type of glucocorticosteroid • glucocorticosteroid dose • duration of treatment (< 7 days or ≥ 7 days) • disease aetiology • presence of relevant comorbidities (diabetes, heart disease, malignancy, chronic lung disease [including COPD], CNS disease [including dementia and cerebrovascular disease] renal failure, alcohol use, COPD) • route of administration • time-to-initiation • age > 75 or ≤ 75.
Intervention	Antibiotic plus glucocorticosteroid for CAP. Antibiotic plus glucocorticosteroid for HAP. Notes: • the choice of antibiotic class and agent should be according to national guidelines • all antibiotics will be pooled • all glucocorticosteroids will be pooled

	• Route of administration for antibiotic may be oral or intravenous and for glucocorticosteroid may be oral, intravenous or by inhalation.
Comparison	Antibiotic plus placebo or antibiotic alone for CAP. Antibiotic plus placebo or antibiotic alone for HAP.
Outcomes	• Mortality (at 30 days). • Length of hospital stay. • Need for ventilatory or ionotropic support (by end of follow-up). • Clinical cure (at end of follow-up) – success or improvement will be accepted as surrogates. • Health-related quality-of-life (by end of follow-up) (measured by CAP symptom questionnaire, EQ5D or SF-36). • Hyperglycaemia (by end of follow-up). • Withdrawal due to treatment-related adverse events. • Complications (by end of follow-up) (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS).
Importance of outcomes	**Critical outcomes:** • mortality • clinical cure • withdrawal due to treatment-related adverse events.
Study design	Systematic reviews and RCTs. • Unit of randomisation: individual patient or hospital/clinic cluster.
Population size and directness	• No restrictions on sample size. • No restrictions on treatment duration. • Studies with indirect populations will not be considered; this includes studies with a mixed population from the HAP and CAP.
Setting	• Secondary care. • Tertiary care. • Community settings in which NHS care is received.
Search Strategy	See appendix
Review Strategy	**Appraisal of methodological quality** • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data** • Meta-analysis will be conducted where appropriate. • Data on all antibiotics within a class will be pooled. • Default MIDs will be used: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes. • For continuous data final and change scores will be pooled and if any study reports both, the method used in the majority of studies will be analysed.
Notes	Note all individual AE frequencies in case needed for HE model. Antibiotics may not be of the same class in control and intervention arm as appropriateness will be determined by treating physician and studies may not specify which antibiotic was used; this is acceptable as long as they state that treatment was according to national guidelines.

6 Gas exchange for patients with community-acquired pneumonia or hospital-acquired pneumonia

6.1 Comparison of non-invasive ventilation, continuous positive pressure ventilation and usual care

Component	Description
Review question	In adults with community-acquired pneumonia or hospital-acquired pneumonia managed in hospital, what is the clinical and cost effectiveness of non-invasive ventilation compared with continuous positive airways pressure or usual care?
Objectives	The aim of this review is to determine the relative clinical and cost effectiveness of NIV, CPAP and usual care in adults with pneumonia managed in hospital.
Population	Adults diagnosed with pneumonia (hospital- or community-acquired): • adult is defined as aged 18 years or over • pneumonia diagnosis made on the basis of chest X-ray • CAP is defined as pneumonia that is acquired outside hospital • HAP is defined as pneumonia that occurs 48 hours or more after hospital admission and is not incubating at hospital admission Studies with mixed HAP/CAP or HAP/VAP populations will be excluded, as will studies exclusively assessing aspiration pneumonia.
Strata	• With and without COPD.
Subgroups	The following groups will be considered separately if data are available: • HAP and high-severity CAP • type 1 compared with type 2 failure. The following factors will be considered for subgroup analysis: • severity score (e.g. APACHE) • eligibility for intubation (note: may be described as critical care or level 3 care) • duration of treatment.
Intervention	• NIV – defining feature is two levels of pressure, whereas CPAP has only one. • CPAP – one set level of pressure and the patient defines the alternate pressure through voluntary respiration.
Comparison	• NIV. • CPAP. • Usual care – oxygen and all other supportive measures, short of assisted ventilation. Note: comparisons of different doses or durations of oxygen will not be included.
Outcomes	• Mortality at 30 days. • Need for intubation/invasive ventilation (tracheostomy or oral endotracheal tube). • Length of hospital (or ITU) stay. • Clinical cure (at end of follow-up) – success or improvement will be accepted as surrogates. • Health-related quality-of-life (measured by CAP symptom questionnaire, EQ5D or SF-36). • Duration of ventilatory assistance.

	• Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS, pneumothorax).
Importance of outcomes	**Critical outcomes:** • mortality at 30 days • need for intubation/invasive ventilation (tracheostomy or oral endotracheal tube) • length of hospital (or ITU) stay.
Study design	Systematic reviews of RCTs and RCTs , comparative observational studies • Unit of randomisation: individual patient or hospital cluster.
Population size and directness	• No restrictions on sample size. • Studies with indirect populations will not be considered unless no other data are available.
Setting	• Secondary care. • Tertiary care.
Search Strategy	See appendix **Intervention terms to include in addition to those listed above**: non-invasive positive pressure ventilation (NPPV or NIPPV), invasive positive pressure ventilation, BiLevel Positive Airway Pressure (BIPAP), non-invasive positive pressure ventilation (NPPV), variable positive airway pressure (VPAP) and AutoPAP and AutoCPAP (APAP, ACPAP). Note: A GDG member highlighted one trial that may be potential source of evidence for inclusion but the population is indirect so was not included (Delclaux C et al. Treatment of acute hypoxemic non-hypercapnoeic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: A randomised controlled trial. JAMA 284(18): 2352-60 (2000)).
Review Strategy	**Appraisal of methodological quality** • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data** • Meta-analysis will be conducted where appropriate; NIV and CPAP will be considered separately. • Default MIDs will be used: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes. • For continuous data final and change scores will be pooled and if any study reports both, the method used in the majority of studies will be analysed.
Notes	Key paper: Zhang Y, Fang C, Dong BR, Wu T, Deng JL. Oxygen therapy for pneumonia in adults. Cochrane Database of Systematic Reviews. 2012; Issue 3:CD006607

6.2 Non-invasive ventilation, continuous positive pressure ventilation or usual care compared with elective intubation

Component	Description
Review question	In adults with community-acquired pneumonia or hospital-acquired pneumonia managed in hospital, what is the clinical and cost effectiveness of non-invasive ventilation, continuous positive airways pressure or usual care compared with elective intubation?
Objectives	The aim of this review is to determine the relative clinical and cost effectiveness of NIV, CPAP or usual care compared with elective intubation in adults with pneumonia managed in hospital.
Population	Adults diagnosed with pneumonia (hospital- or community-acquired): • adult is defined as aged 18 years or over • pneumonia diagnosis made on the basis of chest X-ray • CAP is defined as pneumonia that is acquired outside hospital • HAP is defined as pneumonia that occurs 48 hours or more after hospital admission and is not incubating at hospital admission. Studies with mixed HAP/CAP or HAP/VAP populations will be excluded, as will studies exclusively assessing aspiration pneumonia.
Strata	• With and without COPD.
Subgroups	The following groups will be considered separately if data are available: • HAP and high-severity CAP • type 1 compared with type 2 failure. The following factors will be considered for subgroup analysis: • severity score (e.g. APACHE) • duration of treatment.
Intervention	• NIV – defining feature is two levels of pressure, whereas CPAP has only one. • CPAP – one set level of pressure and the patient defines the alternate pressure through voluntary respiration. • Usual care – oxygen and all other supportive measures, short of assisted ventilation.
Comparison	• Elective intubation. Note: comparisons of different doses or durations of oxygen will not be included.
Outcomes	• Mortality (at 30 days). • Length of hospital (or ITU) stay. • Ventilator-free days. • Clinical cure– success or improvement will be accepted as surrogates. • Health-related quality-of-life (measured by CAP symptom questionnaire, EQ5D or SF-36). • Duration of ventilatory assistance. • Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS, pneumothorax, VAP).
Importance of outcomes	**Critical outcomes:** • Mortality (at 30 days). • Length of hospital (or ITU) stay. • Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS, pneumothorax, VAP).
Study design	Systematic reviews of RCTs or RCTs , comparative observational studies

	• Unit of randomisation: individual patient or hospital cluster.
Population size and directness	• No restrictions on sample size. • Studies with indirect populations will not be considered unless no other data are available.
Setting	• Secondary care. • Tertiary care.
Search Strategy	See appendix **Intervention terms to include in addition to those listed above**: non-invasive positive pressure ventilation (NPPV or NIPPV), invasive positive pressure ventilation, BiLevel Positive Airway Pressure (BIPAP), non-invasive positive pressure ventilation (NPPV), variable positive airway pressure (VPAP) and AutoPAP and AutoCPAP (APAP, ACPAP); immediate intubation, planned initiation of invasive ventilation, or as a surrogate 'intensive care admission'.
Review Strategy	**Appraisal of methodological quality** • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data** • Meta-analysis will be conducted where appropriate; usual care, NIV, CPAP and elective intubation will all be considered separately. • Default MIDs will be used: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes. • For continuous data final and change scores will be pooled and if any study reports both, the method used in the majority of studies will be analysed.
Notes	Key paper: Zhang Y, Fang C, Dong BR, Wu T, Deng JL. Oxygen therapy for pneumonia in adults. Cochrane Database of Systematic Reviews. 2012; Issue 3:CD006607

7 Monitoring for patients with community-acquired pneumonia or hospital-acquired pneumonia

Component	Description
Review question	In adults with community-acquired pneumonia or hospital-acquired pneumonia managed in hospital, what is the clinical and cost effectiveness of C-reactive protein or procalcitonin monitoring in addition to clinical observation in helping to determine when to stop or change treatment and when to discharge?
Objectives	The aim of this review is to determine the predictive accuracy of CRP and PCT in patients hospitalised with pneumonia for determining whether it is safe or appropriate to stop or change antibiotic treatment and to discharge.
Population	Adults diagnosed with pneumonia (hospital- or community-acquired) managed in hospital: • adult is defined as aged 18 years or over • pneumonia diagnosis made on the basis of chest X-ray • CAP is defined as pneumonia that is acquired outside hospital. • HAP is defined as pneumonia that occurs 48 hours or more after hospital admission and is not incubating at hospital admission (inclusion criterion) • low-severity CAP defined by formal assessment or pneumonia managed outside hospital or as an outpatient • moderate- and high-severity CAP defined by formal assessment or pneumonia managed in hospital/ITU. **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.
Subgroups	The following groups will be considered separately if data are available: • CAP and HAP • Low-, moderate- and high-severity CAP. The following factors will be considered for subgroup analysis if heterogeneity is present: • age • co-morbidity (including reason for hospital admission in HAP) • bacterial compared with non-bacterial.
Prognostic factors	Serial measurements or single test after initial admission assessment during the first 5 days for low-severity CAP and 10 days for moderate- to high-severity CAP of: • C-reactive protein • Procalcitonin. All thresholds investigated will be reported to aid identification of the optimum cut-off. **Key confounders:** • CAP severity measured by PSI or CURB65 • age • baseline CRP/PCT • antibiotic therapy before admission • glucocorticosteroid therapy.
Outcomes	• Mortality. • Clinical cure (end of treatment). • Treatment failure.

	• Inappropriate use of antibiotics. • Duration of treatment. • ITU admission or need for invasive ventilation/ionotropic support. • Hospital re-admission (30 days). • Length of hospital stay. • Health-related quality-of-life (up to 30 days). • Complications (including relapse; 30 days).
Importance of outcomes	**Critical outcomes:** • mortality • clinical cure • length of hospital stay • hospital re-admission.
Study design	Systematic reviews and RCTs (test-and-treat studies), prognostic cohort studies**..**
Population size and directness	• No restrictions on sample size. • Studies with indirect populations will not be considered.
Setting	• Secondary care. • Tertiary care.
Search Strategy	See appendix
Review Strategy	**Appraisal of methodological quality** • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data** • Meta-analysis will be conducted where appropriate.
Notes	Consider one-off testing (after baseline assessment) and serial testing for predictive accuracy. CRP tests may be comparing results on day 3 to day 1 whereas PCT may be tested daily. Threshold definitions will be according to study protocols – but differences will be noted. HCAP/NHAP studies will be excluded. Only studies with < 25% NHAP/HCAP patients will be included.

8 Safe discharge for patients with community-acquired pneumonia or hospital-acquired pneumonia

Component	Description
Review question	What is the prognostic value, clinical and cost effectiveness of various factors for assessing whether it is safe to discharge adults with community-acquired pneumonia or hospital-acquired pneumonia requiring management in hospital?
Objectives	The aim of this review is to determine the predictive accuracy of different factors in patients hospitalised with pneumonia for determining whether it is safe or appropriate to discharge.
Population	Adults diagnosed with pneumonia (community - or hospital -acquired) managed in hospital: • adult is defined as aged 18 years or over • pneumonia diagnosis made on the basis of chest X-ray • CAP is defined as pneumonia that is acquired outside hospital. • HAP is defined as pneumonia that occurs 48 hours or more after hospital admission and is not incubating at hospital admission (inclusion criterion). 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.
Subgroups	The following groups will be considered separately if data are available: • CAP and HAP • Low- and moderate- to high-severity CAP. The following factors will be considered for subgroup analysis if heterogeneity is present: • age • comorbidity (including reason for hospital admission in HAP).
Prognostic factors	Physiological scoring systems, including severity assessment tools that are applied before discharge (not at admission). Clinical stability (ability to take antibiotics orally): • normalised heart rate • temperature • systolic BP • oxygen saturation • mental status. Key confounders: • CAP severity measured by PSI or CURB65 • age • do-not-resuscitate status.
Outcomes	• Mortality (30 days). • Hospital re-admission. • Health-related quality-of-life. • Activities of daily living. • Complications (including relapse, empyema, effusion, abscess, metastatic infection, superinfection, MODS).
Importance of outcomes	**Critical outcomes:** • mortality

Component	Description
	• health-related quality-of-life • hospital re-admission.
Study design	**RCTs (test and treat studies), prognostic cohort studies or systematic reviews.**
Population size and directness	• No restrictions on sample size. • Studies with indirect populations will not be considered.
Setting	Hospital.
Search Strategy	See appendix
Review Strategy	**Appraisal of methodological quality** The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data** Meta-analysis will be conducted where appropriate.
Notes	Include studies that assess whether it is necessary to wait for at least 24 hours remaining afebrile after intravenous to oral switch before discharge. RCTs may compare e.g. a set of stable patients randomised to waiting 24 before discharge or no wait and discharge. Markers of stability all feed in to decision to discharge as independent variables. Both multivariate and univariate analyses will be included. **Key papers**: Halm EA, Fine MJ, Kapoor WN, Singer DE, Marrie TJ, Siu AL. Instability on hospital discharge and the risk of adverse outcomes in patients with pneumonia. Archives of Internal Medicine. 2002; 162(11):1278-1284. Aliberti S, Zanaboni AM, Wiemken T, Nahas A, Uppatla S, Morlacchi LC, Peyrani P, Blasi F, Ramirez J. Criteria for clinical stability in hospitalised patients with community-acquired pneumonia. Eur Respir J. 2013 Sep;42(3):742-9.

9 Patient information for patients with community-acquired pneumonia or hospital-acquired pneumonia

Component	Description
Review question	What advice should be given to adults about what symptoms and duration of symptoms can be expected following treatment for community-acquired or hospital-acquired pneumonia, and when should patients be advised to consult or re-consult a GP?
Objectives	The aim of this review is to establish the most common symptoms and their standard duration in patients with pneumonia in order to provide advice to patients.
Population	Adults diagnosed with pneumonia (hospital- or community-acquired).
Subgroups	The following groups will be considered separately if data are available: • CAP and HAP • low-, moderate- and high-severity CAP. The following factors will be considered for subgroup analysis if heterogeneity is present: • age • co-morbidity (including reason for hospital admission in HAP) • managed in hospital or in the community.
Outcomes	• Proportion with specific symptoms and time to resolution of these symptoms at specific time points after diagnosis. • Alteration or additional course of antibiotics after discharge from hospital or initial primary care consultation. • Re-consultation (pneumonia-related). • Change in quality-of-life (including symptom domains). • Return to usual activities or activities of daily living.
Importance of outcomes	Critical outcomes: • re-consultation (pneumonia-related) • Proportion with specific symptoms and time to resolution of these symptoms at specific time points after diagnosis.
Study design	Systematic reviews, observational studies (ideally large cohorts), qualitative studies (natural history data, patient reported outcomes). RCTs will only be considered if no cohort data are available (because the highly selected population in trials will be less applicable for this review question).
Population size and directness	• No restrictions on sample size. • Studies with indirect populations will not be considered.
Setting	• Community or discharged from hospital.
Search Strategy	See appendix
Review Strategy	**Appraisal of methodological quality** • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. **Synthesis of data** • Narrative summary will be undertaken.

10 Health economic

Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to the review questions set out above.
Criteria	• Populations, interventions and comparators must be as specified in the individual review protocols above. • Studies must be of a relevant economic study design (cost–utility analysis, cost–benefit analysis, cost-effectiveness analysis, cost–consequence analysis, comparative cost analysis). • Studies must not be an abstract only, a letter, editorial or commentary, or a review of economic evaluations.[(a)] Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix F.
Review strategy	Each study fulfilling the criteria above will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the NICE guidelines manual (2012).[1] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim is to include studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the GDG if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix K. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden) • OECD countries with predominantly private health insurance systems (for example, USA, Switzerland) • non-OECD settings (always 'Not applicable'). *Economic study type:* • cost–utility analysis • other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequence analysis)

	• comparative cost analysis • non-comparative cost analyses including cost-of-illness studies (always 'Not applicable'). *Year of analysis:* • The more recent the study, the more applicable it is. • Studies that are based on resource use and unit costs from more than [10] years ago will be downgraded in terms of applicability. *Quality and relevance of effectiveness data used in the economic analysis:* • The more closely the effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

11 References

1 National Institute for Health and Clinical Excellence. The guidelines manual. London: National Institute for Health and Clinical Excellence; 2012. Available from: http://publications.nice.org.uk/the-guidelines-manual-pmg6/