Managing Common Infections

Pneumonia (hospital-acquired): antimicrobial prescribing

Stakeholder comments table

12/02/2019 – 11/03/2019

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1	The British Society for Antimicrobial Chemotherapy	Guideline	General		It appears these guidelines were not written by infection specialists as there is no antimicrobial stewardship present.	Thank you for your comment. The full list of the committee members responsible for the development of this guideline is available on the NICE website on the guideline landing page. The committee is made up of general practitioners, microbiologists, antimicrobial pharmacists, antimicrobial prescribing guideline developers and other infection specialists who have expertise in and considered the implications of antimicrobial stewardship when developing this guideline.
2	The British Society for Antimicrobial Chemotherapy	Guideline	General		~~T~~oo many quinolone/C-drug options ~~for my liking~~ as most hospitals have moved away from cephalosporin prescribing in adults. Scottish hospitals have C-drugs monitored and this guidance, if adopted, would be a step backwards.	Thank you for your comment. The committee has discussed your comment and the guideline has been amended. The committee concluded that, based on the evidence considered, cephalosporins remain an appropriate antibiotic choice for hospital-acquired pneumonia but appreciated the need for greater consideration of other choices. As such, the prescribing table now emphasises that antibiotic choice should be based on local resistance data and specialist microbiological advice.

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3	The British Society for Antimicrobial Chemotherapy	Guideline	General		Antipseudomonals apart from aminoglycosides should be available on discussion only with microbiologists to preserve their utility. Otherwise this leads to increasing reliance on ceftaz/avibactam.	Thank you for your comment. No changes have been made to antibiotic choices in the antibiotic prescribing table, however the committee decided to add that these options should be available based on specialist microbiological advice only.
4	The British Society for Antimicrobial Chemotherapy	Guideline	General		Guidance does not take into account different antimicrobial susceptibilities across different trusts/health boards. Where ESBLs & AMPCs dominate the HAPS other antibiotics should be used: Aminoglycosides, Cotrimoxazole and Temocillin.	Thank you for your comment. The committee discussed your comments and are of the opinion that the current recommendations acknowledge the need to take account of local antimicrobial resistance data. The committee agreed to amend the prescribing tables to acknowledge that other antibiotic choices are appropriate, based on local resistance data and specialist microbiological advice only.
5	The British Society for Antimicrobial Chemotherapy	Guideline	General		The evidence presented in the guidelines relies heavily on one paper which has a major drawback in that its approach breeds further resistant isolates.	Thank you for your comment. Appendix D in the evidence review outlines that a total of 9 studies were identified (from an initially identified 15691) which were considered and along with committee discussions on the evidence informed the development of this guideline. All of the evidence has been considered and discussed by the committee in the development of the guideline as outlined in the interim process and methods guide for antimicrobial prescribing guidelines. The committee based their decisions on evidence, experience as well as the consideration of antimicrobial stewardship and resistance. The rationale for antibiotic choice is detailed in the guideline.

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6	The British Society for Antimicrobial Chemotherapy	Draft guideline: visual summary	1	Box 1	Question 4: We note that whilst it is ideal to obtain a respiratory sample prior to initiating therapy, the reality is that many patients are not expectorating or productive and a good quality diagnostic sample in non-ventilated ward-based patients is not often obtained.	The committee discussed your comment and agreed to remove 'respiratory' to allow clinicians to choose the most appropriate sample.
7	The British Society for Antimicrobial Chemotherapy	Draft guideline	1	Box 'prescribing considerations'	We believe that these are the fundamental clinical principles that should guide therapy/management and should include a statement on establishing the clinical diagnosis of HAP i.e. CXR changes consistent with pneumonia. In our clinical experience, we often find the label of 'HAP' applied to deteriorating in-patients who are short of breath or have an oxygen requirement +/- temperature for other clinical reasons, with no CXR evidence of consolidation.	Thank you for your comment. The committee recognised the importance of diagnosis, but its consideration is outside the scope of this guideline. NICE recognises the importance of diagnosis which was considered in Pneumonia in adults: diagnosis and management: Clinical guideline [CG191] and the lack of identified evidence regarding diagnosis in hospital-acquired pneumonia prompted the development of a research recommendation. This guideline was reviewed November 2018 and no new evidence has been identified with which to inform recommendations in this area. This will be reviewed again in due course. A definition of hospital-acquired pneumonia is included in this guideline, which is taken from NICE clinical guideline Pneumonia in adults: diagnosis and management: Clinical guideline [CG191].
8	The British Society for Antimicrobial Chemotherapy	Draft guideline	General		We are concerned about the resignation of Kieran Hands and Peter Jenks from the guideline committee. Furthermore, we are concerned about the lack of secondary care clinical expertise, including Respiratory physicians, on the guideline committee.	Thank you for your comment. The full list of the committee members responsible for the development of this guideline is available on the NICE website on the guideline landing page. The committee is made up of general practitioners, microbiologists, antimicrobial pharmacists, antimicrobial prescribing guideline developers and other infection

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						specialists who have expertise in and considered the implications of antimicrobial stewardship when developing this guideline. This guideline has also been reviewed by two respiratory topic experts, Tim Felton and Richard Barraclough.
9	The British Society for Antimicrobial Chemotherapy	Draft guideline	4	5	Question 4: we are extremely concerned about the suggested empirical antibiotic choices for severe symptoms. In our opinion, this should be at the discretion of local teams based on their local epidemiology and patient cohort as we do not believe that it is possible to produce a national guideline that covers all patients and all scenarios. In our view, it would be better to emphasise the principles of approach to diagnosis and management in the individual patient as described above in comment 2. The choices of piperacillin/tazobactam, meropenem, ceftriaxone and ceftazidime are **far too broad** for the majority of non-ventilated patients with HAP. This is certainly the case for our large 1,700 bed tertiary referral centre. Ceftazidime does not have adequate S. pneumoniae and S. aureus cover. Empirical treatment for P. aeruginosa HAP would need to be based on the presence of underlying structural lung disease or post mechanical ventilation or presence of trachaeostomy etc Locally, for severe HAP we advise co-trimoxazole 1.44g bd 1st line, po levofloxacin 500mg bd 2nd line and IV cefuroxime (switching to oral doxycycline) 1.5g tds 3rd line to ensure empirical cover for S. pneumoniae, which is still the leading cause of HAP.	Thank you for your comment. The committee discussed your comment and noted that recommendations highlight the need to take account of local hospital and ward-based antimicrobial resistance data when choosing an antibiotic. The antibiotics in this section remain in the table, but information has been added that indicates that these antibiotic choices are options and choice should be based on local resistance data and specialist microbiological advice only. The committee has considered your comment regarding adequate S. pneumoniae cover and has added co-trimoxazole as an antibiotic choice in the guideline.

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10	The British Society for Antimicrobial Chemotherapy	Draft guideline	4	5	Question 4: there is no mention of assessing for/considering possible aspiration pneumonia and considering the need for anaerobic cover (if not provided by the initial empirical antibiotic choice).	Thank you for your comment. The committee discussed this comment and agreed that aspiration pneumonia is excluded from this guideline. The committee considered it a distinct clinical condition which requires anaerobic antibiotic cover which would result in the inappropriate prescribing of broad spectrum antibiotics if this guideline was followed.
11	Scottish Antimicrobial Prescribing Group	Visual summary and guideline	General		General points We agree with much of the text and the principles of management of “HAP” – shorter duration and early review and IVOST. Agree there is no consensus on severity assessment in HAP and this needs to be based on clinical judgement. It is difficult to judge the recommendations on treatment when the guidance acknowledges they have not defined the patient population. This must be possible if they are citing clinical trial data which defines the patient populations very clearly. There is discussion in the evidence about timing of onset and differences in pathogens but the actual recommendations lump all together if onset of symptoms >48 hours post admission. There is no acknowledgement that HAP is frequently over diagnosed which has major implications for antibiotic use as the guidance is promoting generally broad spectrum treatment. It is worth adding that as the diagnosis of HAP is often inaccurate an important part of the antibiotic / patient management pathway is the clinical review. Is the diagnosis right?	Thank you for your comments. The patient population are adults, young people and children with hospital-acquired pneumonia which was pre-defined in the research protocol that underpins the systematic review of evidence used to inform the guideline. Hospital-acquired pneumonia is defined in the guideline. The recommendations are made based on the identified evidence and committee expertise in line with the ‘interim process and methods guide for antimicrobial prescribing guidelines’. Given the paucity of data it would be inappropriate to make specific recommendation based solely on the trial data as it may not appropriately reflect the UK context in line with the scope of this guideline. Furthermore, the evidence suggested that there was no difference in the efficacy of antibiotics for the treatment of hospital acquired pneumonia. The committee discussed your comments and the prescribing table has been amended for clarity. Prescribers should follow the NICE antimicrobial guideline on

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					There is no mention of C.diff risk which is an important consideration in what is potentially an elderly and frail population. All the recommended antibiotics within this guideline are demonstrably higher risk of C. diff and we don't think it is adequate to link to other NICE guidance on stewardship. The C.diff risk must be explicit. The evidence base for IV therapy is review of published comparative trials. This evidence may be flawed as it is based on trials of new agents versus the perceived "gold standard". Understandably broad spectrum agents usually with anti-Pseudomonal activity are chosen for these study comparators. This should be acknowledged in the discussion/text. A long list of broad spectrum antibiotics is not very helpful without carefully worded caveats Choice of antibiotic for both severe and non-severe HAP is speculative given lack of consensus on diagnosis, lack of studies for non-severe HAP and nature of the RCTs in severe HAP. HAP is often misdiagnosed, I note use of CXR has been the sentence "When managed in hospital, the diagnosis is usually confirmed by chest X ray." However otherwise this guidance does not give sufficient steer on the diagnosis of HAP. Blood cultures are not mentioned (respiratory sampling is), given the over-diagnosis of HAP use of blood cultures should be promoted, where appropriate – sepsis with organ dysfunction, febrile, starting IVs etc. The paper distinguishes HAP as pneumonia after 48 hours but early onset as <4 days so should we continue	community-acquired pneumonia for choices of antibiotics for people with pneumonia and onset of symptoms within 48 hours of hospital admission – as this does not meet the definition for hospital-acquired pneumonia. For people with the onset of symptoms on days 3 to 5 of hospital admission and not at higher risk of resistance, prescribers should consider following the NICE antimicrobial guideline on community-acquired pneumonia for choices of antibiotics. This guideline includes amoxicillin as a first choice antibiotic for adults with low and moderate severity symptoms and children and young people with non-severe symptoms. The committee acknowledged the difficulties in hospital-acquired pneumonia diagnosis and the guideline acknowledges the lack of validated severity assessment tools for hospital-acquired pneumonia. The committee recognised the importance of diagnosis, but its consideration is outside the scope of this guideline. NICE recognise the importance of diagnosis which was considered in Pneumonia in adults: diagnosis and management: Clinical guideline [CG191] and the lack of identified evidence regarding diagnosis in hospital-acquired pneumonia prompted the development of a research recommendation. This guideline was reviewed November 2018 and no new evidence has been identified with which to

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					to use CAP guidance in patients in hospital for <4 days who develop pneumonia. Some of the guidance – treat with IVs for 48 hours in severe infection and minimum of 5 days does not promote “review and revise” the diagnosis by a senior decision maker, there is good guidance to review microbiological samples and review antibiotic choices but the guidance is so long much of this will be missed.	inform recommendations in this area. This will be reviewed again in due course. The committee discussed your comments regarding *Clostridium difficile* and recommendations have been amended to make specific reference to the consideration of the risk of *Clostridium difficile* infection amongst other adverse effects when choosing broad spectrum antibiotics. The table now includes co-trimoxazole, doxycycline, cefalexin and levofloxacin as alternative antibiotic choices in penicillin allergy for people with non-severe symptoms or signs. Hospital-acquired pneumonia is a serious infection that requires effective treatment with a broad spectrum antibiotic, and antibiotic choice should be based on local resistance data and specialist microbiological advice. All of the evidence identified in the evidence review that underpins the guideline is assessed for risk of bias and each outcome is quality assessed using GRADE, as per the interim process and methods guide for antimicrobial prescribing guidelines. This was considered during committee discussions and reflected in the guideline recommendations. The committee discussed your comment on samples for microbiological testing. The guideline has been amended and reference to ‘respiratory’ has been removed.

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						The committee discussed your comments regarding “review and revise” and the prescribing table has been amended to review intravenous antibiotics by 48 hours and consider switching to oral antibiotics as above for a total of 5 days then review.
12	Scottish Antimicrobial Prescribing Group	Visual summary and guideline	General		Antibiotic choice On page 16 it states first choice IV antibiotics for those with severe symptoms and this section concludes with ‘.These broad spectrum antibiotics have good activity against common pathogens in this population, including multi-drug resistant Pseudomonas aeruginosa, ESBLs and some carbapenemase-producing gram negative bacteria’. We disagree with some of this advice: • Ceftriaxone and cefuroxime do not cover Pseudomonas aeruginosa or ESBLs but highlighted statement suggests otherwise. • Would not favour ceftazidime as first line empirical option given poor option for Gram positive bacteria which may be pathogen. • Unclear why Ceftazidime avibactam is included given would be on specialist advice and unlikely to be considered first line in most hospitals. Would a comment on discussion with specialist if high risk or known carbapenemase producing organism carriage be more suitable? Levofloxacin dose should be 500mg bd if wishing to cover pathogens such as S. pneumoniae and P. aeruginosa Would be useful to have mention of doxycycline which is included in many policies in the UK. Understand that doxycycline does not cover more	Thank you for your comment. The committee has discussed your comments and some amendments have been made to the guideline. Recommendations outline the need to consider a number of factors when choosing an antibiotic including local hospital and ward-based antimicrobial resistance data, and recent microbiological results. The prescribing table has been amended to outline that for first choice IV antibiotics for hospital-acquired pneumonia with severe symptoms or signs, or for individuals at higher risk of resistance the antibiotic choices outlined represent a list of possible empirical options, but antibiotic choice should be based on local resistance data and specialist microbiological advice. The committee has amended the prescribing table and replaced cefuroxime with cefalexin as availability and oral absorption were both considered to be more favourable. The statement regarding coverage refers to all the broad spectrum antibiotics in the list of which all are judged to have good activity against common

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					resistant Gram negatives/Pseudomonas but similar case could be made against co-amoxiclav with rising R rates in enterobacterales but is still included in guideline for non-severe infection. It is difficult to promote one antibiotic over another when local resistance rates and epidemiology of hospitalised patients varies considerably within and between areas. Associated additional risks of fluoroquinolones, that have been recently highlighted, are not acknowledged.	pathogens for hospital-acquired pneumonia. This has been edited to make this clearer The committee has considered your comments in light of recent MHRA safety warnings regarding the use of fluoroquinolones. Levofloxacin remains in the prescribing table as the committee considered it a good alternative option for treating hospital-acquired pneumonia with non-severe symptoms or signs when co-amoxiclav is unsuitable and as a choice for hospital-acquired pneumonia with severe symptoms or signs. Safety considerations of fluoroquinolones are outlined in footnotes to the prescribing table and in the medicines safety section of the guideline. The committee has discussed your comment regarding doxycycline: Doxycycline has been added as an alternative antibiotic option for non-severe symptoms, for penicillin allergic individuals or if co-amoxiclav is unsuitable. Information has also been added that outlines that these antibiotic choices are options and choice should be based on local resistance data and specialist microbiological advice.
13	Scottish Antimicrobial Prescribing Group	Q2	General		Implementation In Scotland this guidance would be challenging to implement as it is reliant on broad spectrum antibiotics with high risk of CDI.	Thank you for your comment. The committee discussed your comments regarding *Clostridium difficile* infection and recommendations have been amended to make specific reference to the consideration of the risk of *Clostridium difficile* infection amongst other adverse effects when

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						choosing broad spectrum antibiotics. Hospital-acquired pneumonia is a serious infection that requires effective treatment with a broad spectrum antibiotic, based on local resistance data and specialist microbiological advice.
14	British Thoracic Society				Thank you for inviting comments from the British Thoracic Society.	Thank you and we welcome your contribution.
15	British Thoracic Society	Guideline	General		"The committee also agreed that recent antibiotic use (within the last 3 months) and recent healthcare exposure before the current hospital admission were also highly likely to increase the risk of resistant pathogens" This statement is based on predominantly US data and UK and European data suggest a very low prevalence of drug resistant pathogens in this patient group. We suggest the panel remove this statement (even the US guidelines have recently acknowledged that this "Healthcare associated pneumonia" concept is unhelpful and removed it from their guidelines).	Thank you for your comment. The committee discussed your comments and have clarified that recent use of antibiotics relates to the use of broad spectrum antibiotics. Based on its experience the committee agreed that this would be likely to increase the risk of resistant pathogens.
16	British Thoracic Society	Guideline	General		The lack of evidence is reflected in the very broad choices in antibiotics. It may be helpful to add a statement to review the diagnosis as a lot of "HAP" patients turn out to have something other	Thank you for your comment. The committee based its recommendations on the identified evidence, its experience, antimicrobial stewardship and antimicrobial resistance. The committee decided that it was appropriate to provide options with adequate coverage, and that decisions to

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					than HAP so that de-escalation of antibiotics is very important.	prescribe a treatment would be based on local resistance data and specialist microbiological advice. The committee recognised the importance of diagnosis, but its consideration is outside the scope of this guideline. NICE recognise the importance of diagnosis which was considered in Pneumonia in adults: diagnosis and management: Clinical guideline [CG191] and the lack of identified evidence regarding diagnosis in hospital-acquired pneumonia prompted the development of a research recommendation. This guideline was reviewed November 2018 and no new evidence has been identified with which to inform recommendations in this area. This will be reviewed again in due course. The guideline provides recommendations regarding reassessment and specialist advice which provide recommendations on reviewing antibiotic choice and regimen when microbiological results are available, if symptoms do not improve as expected or worsen and scenarios when you may need to seek specialist advice.
17	British Thoracic Society		1.1.8		We are pleased to note the inclusion of the reference to the NICE “care of dying adults” is highlighted in this population.	Thank you for your comment.
18	UK Clinical Pharmacy Association	Guideline	4		In practice, ceftazidime/avibactam would only be initiated for this indication if there was confirmed resistant pathogens after MDT approval, because of its broad-spectrum use + cost implications. By	Thank you for your comment. The committee has discussed your comments and the prescribing tables have been amended to emphasise that for first choice

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					incorporating it within this guidance, will it un-intentionally promote its use?	intravenous antibiotics for hospital-acquired pneumonia with severe symptoms or signs or for individuals at higher risk of resistance, decisions should be based on local resistance data and specialist microbiological advice only.
19	UK Clinical Pharmacy Association	Guideline	4		Meropenem is listed in the guidance for severe infections or higher risk of resistance – in practice the 1g TDS would prescribed over 500mg TDS.	The committee discussed your comment regarding the dosing of meropenem and no change has been made. A dosing range has been provided that is in line with the British National Formulary.
20	UK Clinical Pharmacy Association	Guideline	4		Cefuroxime is listed in the guidance for severe infections or higher risk of resistance – in practice the 1.5g TDS would prescribed over 750mg TDS.	Thank you for your comment. The committee discussed the dosage of cefuroxime in adults when using it as a first choice IV antibiotic for hospital-acquired pneumonia with severe symptoms or signs, or for individuals at higher risk of resistance, and agreed not to make any changes. The dosage is in line with the British National Formulary, and the dose range allows individual choice based on, for example, the severity of infection.
21	UK Clinical Pharmacy Association	Guideline	General		Disappointing that the recommendation is for high CDI risk/Reserve in AWaRe antibiotics rather than doxycycline.	Thank you for your comment. The committee discussed your comment regarding *Clostridium difficile* infection and recommendations have been amended to make specific reference to the consideration of the risk of *Clostridium difficile* infection amongst other adverse effects when choosing broad spectrum antibiotics. Hospital-acquired pneumonia is a serious infection that requires effective treatment with a broad spectrum antibiotic, based on local resistance data and specialist microbiological advice.

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						The committee has discussed your comment regarding doxycycline and has amended the prescribing table. Doxycycline has been added as an alternative antibiotic option for non-severe symptoms, for penicillin allergic individuals or if co-amoxiclav is unsuitable. Information has also been added that outlines that these antibiotic choices are options and choice should be based on local resistance data and specialist microbiological advice.
22	UK Clinical Pharmacy Association	Guideline	General		The difficulty in diagnosing HAP should be highlighted.	Thank you for your comment. The committee recognised the importance of diagnosis, but its consideration is outside the scope of this guideline. NICE recognise the importance of diagnosis which was considered in Pneumonia in adults: diagnosis and management: Clinical guideline [CG191] and the lack of identified evidence regarding diagnosis in hospital-acquired pneumonia prompted the development of a research recommendation. This guideline was reviewed November 2018 and no new evidence has been identified with which to inform recommendations in this area. This will be reviewed again in due course.
23	UK Clinical Pharmacy Association	Guideline	General		Recommendation for 5 day course of antibiotics is welcome.	Thank you for your comment
24	UK Clinical Pharmacy Association	Guideline	General		Clostridium difficile infection is not mentioned and this is considered important as some broad spectrum antibiotics are recommended.	Thank you for your comment. The committee discussed your comments regarding *Clostridium difficile* infection and recommendations have been amended to

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						make specific reference to the consideration of the risk of *Clostridium difficile* infection amongst other adverse effects when choosing broad spectrum antibiotics.
25	UK Clinical Pharmacy Association	Guideline	4-5		Many of the treatment options for severe HAP should only be used on infection specialist advice.	Thank you for your comment. The prescribing table has been amended to emphasise that antibiotic choice should be based on local resistance data and specialist microbiological advice only.
26	UK Clinical Pharmacy Association	Guideline	5		Recommendation for double dose co-amoxiclav in children 1-5 years - in practice to aid compliance 5ml of the 250mg/5ml suspension is often prescribed. Appreciate this is not recommended in the BNF-C but should be considered as is common practice in paediatric centres. Where has the evidence for using double dose come from?	Thank you for your comment. The dosage presented in the table is in line with the British National Formulary for children. However, the committee discussed your comment and agreed to add a footnote to indicate that 5 ml of co-amoxiclav 250/62 suspension could also be used.
27	UK Clinical Pharmacy Association	Guideline	7		Interesting that PO cefuroxime has been recommended for use in children – in practice this is not commonly prescribed in children and hence certainly the suspension is not routinely stocked in community / paediatric hospital pharmacies.	Thank you for your comment. The committee discussed your comment and the prescribing table has been amended. Oral cefuroxime has been replaced by oral cefalexin which the committee considered to have better availability and oral absorption.
28	UK Clinical Pharmacy Association	Guideline	6		Rather than recommending IV piperacillin/tazobactam could IV co-amoxiclav plus gentamicin be considered?	Thank you for your comment. The committee was aware that IV co-amoxiclav plus gentamicin is used as an option for hospital acquired pneumonia. After discussion the committee decided not to recommend IV co-amoxiclav plus gentamicin as no evidence was identified and concerns were raised regarding possible ototoxicity and nephrotoxicity. Based on committee discussions the prescribing table has been amended to

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						outline that first choice IV antibiotics for hospital-acquired pneumonia with severe symptoms or signs, and for individuals at higher risk of resistance should be based on local resistance data and specialist microbiological advice only, with the list of antibiotics outlined as options.
29	Neonatal & Paediatric Pharmacists Group	Guideline	p16		The antibiotic choice is very prescriptive, in particular the cephalosporin choice. Following discussions with members across several organisations within the UK, it became apparent that none of us keep oral cefuroxime. Should there be more than 1 cephalosporin to choose from to take into account local purchasing decisions or local resistance patterns?	Thank you for your comment. The committee discussed your comments and the prescribing table has been amended. Oral cefuroxime has been replaced by oral cefalexin which the committee considered to have better availability and oral absorption. The prescribing table now states that antibiotic choice should be based on local resistance data and specialist microbiological advice only.
30	Neonatal & Paediatric Pharmacists Group	Guideline	p15-6		Was there any evidence to suggest addition of gentamicin in severe illness with *Pseudomonas aeruginosa*?	Thank you for your comment. The committee was aware that gentamicin is used as an option but decided not to recommend it as no evidence was identified and concerns were raised regarding possible ototoxicity and nephrotoxicity. The committee discussed your comment and based on their experience the committee did not add gentamicin as a treatment option because the antibiotics recommended in the prescribing table were felt to provide adequate coverage.
31	Neonatal & Paediatric Pharmacists Group	Guideline	p15-16		Should duration of treatment be extended in cases of severe illness with *Pseudomonas aeruginosa*?	Thank you for your comment. The committee discussed your comments and are of the opinion that the recommendations provide sufficient scope to make a clinical decision on whether to extend a treatment or not based on severity of hospital-acquired

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						pneumonia. The recommendations outline that reassessment should occur if there is no improvement or individual worsens rapidly or significantly. Recommendations also outline that specialist advice should be sought. At this stage, based on the individual needs of the patient and clinical judgement a decision to extend treatment may occur.
32	Royal College of Physicians	General	General		The RCP is grateful for the opportunity to respond to the above consultation. In doing so we would like to endorse the response submitted by the British Thoracic Society (BTS). We have also liaised with our Joint Specialty Committee for Infectious Disease and would like to make the following comments.	Thank you and we welcome the RCPs contribution.
33	Royal College of Physicians	General	General	l	In terms of treatment, the use and duration of use of macrolides could be more restrictive, partly because of the risk of driving antimicrobial resistance and partly because of drug interactions (mainly with statins). The evidence that macrolides, when given in addition to beta-lactams, improve outcomes is pretty scarce. The argument that they are needed for atypical organisms is weak as atypical pneumonia is relatively uncommon.	Thank you for your comment. The committee discussed your comment. The choice of antibiotics takes account of the balance between risks and benefits and the committee agreed that macrolides (clarithromycin) are an appropriate alternative first choice oral treatment for children and young people who are penicillin allergic or for whom co-amoxiclav is unsuitable but did not recommend a macrolide (clarithromycin) for adults. The committee felt that cefalexin represented a better empirical choice in adults as clarithromycin does not provide cover for gram negative pathogens. All antibiotic choices should be based on local resistance data and specialist microbiological advice.

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34	Royal College of Physicians	General	General		Our experts believe the guidance should also emphasise the taking of blood cultures before administering antibiotics, especially in nosocomial pneumonia (some cases of pneumonia will be bacteraemic and some nosocomial cases might be misdiagnosed as pneumonia).	Thank you for your comment. The committee discussed your comment on samples for microbiological testing. The committee recognised the importance of diagnosis, but its consideration is outside the scope of this guideline. NICE recognise the importance of diagnosis which was considered in Pneumonia in adults: diagnosis and management: Clinical guideline [CG191] and the lack of identified evidence regarding diagnosis in hospital-acquired pneumonia prompted the development of a research recommendation. This guideline was reviewed November 2018 and no new evidence has been identified with which to inform recommendations in this area. This will be reviewed again in due course.
35	Royal College of Physicians	General	General		Our experts believe the suggestion about sending sputum samples should be removed. Sputum is rarely useful in the context of acute pneumonia, sputum assessment in the labs adds to workload without any useful information being provided and, if sputum tests are done, might lead to overuse of antibiotics.	Thank you for your comment. The committee has discussed your comment and acknowledge the issues regarding obtaining a sample, however they feel that it remains a useful guide (in addition to other factors) when choosing the most appropriate treatment. The list of examples is not intended to be comprehensive.
36	Royal College of Physicians	General	General		The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our Joint Specialty Committee for Infectious Disease and would like to make the following comment.	Thank you and we welcome the RCPs and their Joint Specialty Committee for Infectious Disease's contribution
37	Royal College of Physicians	General	General		In terms of treatment, the use and duration of use of macrolides could be more restrictive, partly	Thank you for your comment. The committee discussed your comment. The

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					because of the risk of driving antimicrobial resistance and partly because of drug interactions (mainly with statins). The evidence that macrolides, when given in addition to beta-lactams, improve outcomes is pretty scarce. The argument that they are needed for atypical organisms is weak as atypical pneumonia is relatively uncommon.	choice of antibiotics takes account of the balance between risks and benefits and the committee agreed that macrolides are an appropriate alternative first choice oral treatment for children and young people who are penicillin allergic or for whom co-amoxiclav is unsuitable. Macrolides are not recommended in addition to a beta-lactam antibiotic in this guideline.
38	Royal College of Physicians	General	General		Our experts believe the guidance should also emphasise the taking of blood cultures before administering antibiotics, especially in nosocomial pneumonia (some cases of pneumonia will be bacteraemic and some nosocomial cases might be misdiagnosed as pneumonia).	Thank you for your comment. The committee discussed your comment on samples for microbiological testing. The committee recognised the importance of diagnosis, but its consideration is outside the scope of this guideline. NICE recognise the importance of diagnosis which was considered in Pneumonia in adults: diagnosis and management: Clinical guideline [CG191] and the lack of identified evidence regarding diagnosis in hospital-acquired pneumonia prompted the development of a research recommendation. This guideline was reviewed November 2018 and no new evidence has been identified with which to inform recommendations in this area. This will be reviewed again in due course.
39	Royal College of Paediatrics and Child Health (on behalf of the British Paediatric	NICE hospital-acquired pneumonia	General		Overall, the guideline reflects clinical practice in children	Thank you for your comment

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	Respiratory Society)					
40	Royal College of Paediatrics and Child Health (on behalf of the British Paediatric Respiratory Society)	NICE hospital-acquired pneumonia	1.2(5)	4	There is not a distinction made between the use of cefuroxime and other broader spectrum antipseudomal antibiotics such as Piptaz, most would not consider these equivocal in terms of treating hospital acquired pneumonia	Thank you for your comment. The part of table 1 you refer to is the list of possible first choice IV treatment options for hospital-acquired pneumonia if there are severe symptoms or signs. These are the antibiotic choices that the committee felt were appropriate based on its experience and the evidence. The prescribing table has been amended to make it clear that the choice of IV antibiotic treatment should be led by local resistance data and specialist microbiological advice.
41	Correvio Ltd.	Guideline	4	Table 1	The choice of using the indicated molecules for the treatment of adult patients at risk of severe symptoms may not take into account co-morbid conditions which may limit the use of certain molecules, as bactericidal and safer choices may be required. For example, specific subgroups of patients may benefit from newer molecules; in particular frail/elderly patients at risk of poor outcome. In the post-hoc exploratory study analysing data from two pivotal trials, ceftobiprole treated patients presenting with >10 comorbidities, with high-risk severity scores, treated in the ICU, or with concurrent bacteraemia showed numerical superiority, indicating potential benefit from the 5th generation molecule treatment over combination/dual therapies [Scheeren, et al. BMC Infect Dis 2019 ;19(1):195]. Specifically, in HAP patients, potential for improved clinical outcomes (early clinical response) with ceftobiprole compared with the active-control therapy	Thank you for your comment. The committee has discussed your comment and based on the evidence has not specifically recommended ceftobiprole. However, the prescribing table has been amended to include a list of options, with antibiotic choice being based on local resistance data and specialist microbiological advice only. The Awad et al (2014) RCT which the Scheeren et al. (2019) study undertakes a post-hoc analysis of, has been identified and included in the hospital-acquired pneumonia evidence review. The findings of the sub-group analysis indicated no significant difference between ceftobiprole and ceftazidime plus linezolid in people with non-ventilator-associated hospital-acquired pneumonia.

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					(ceftazidime plus linezolid) were seen in in the overall high-risk patient group (treatment difference 12.5%, 95% CI, 3.5, 21.4), as well as in HAP patients with >10 baseline comorbidities compared with patients who received the double active-control therapy (treatment difference 15.3%, 95% CI, 0.3, 30.4). Overall, differences in outcome (clinical cure at TOC, 30-day all-cause mortality, early clinical improvement) >10% in specific risk-groups were also observed. Between treatment differences of >10% in the proportion of high-risk patients with early clinical improvement were observed in patients with any Gram-positive pathogen (14.8%), any Gram-negative pathogen (11.8%) or any *S. aureus* (23.0%) in the CE population whereas in the ITT population, between treatment differences of >10% were observed in patients with >10 comorbidities (11.9%, favouring ceftobiprole; 95% CI − 1.4, 24.9), in patients with any MRSA (14.9%, favouring ceftobiprole; 95% CI − 9.1, 38.8) and in patients with any *P. aeruginosa* (14.8%, favouring ceftobiprole; 95% CI − 9.2, 38.9). All-cause mortality at 30 days, differences in mortality rate of >10% were observed in high-risk HAP patients with any Gram-positive pathogen (− 11.2%; favouring ceftazidime plus linezolid; 95% CI − 23.1, 0.7) or with any *S. aureus* (− 12.5%; favouring ceftazidime plus linezolid; 95% CI − 28.4, 3.5) in the CE population, whereas in the ITT population, between-treatment difference of >10% in 30-day all-cause mortality was observed in patients with bacteraemia in the HAP study (− 16.2%, favouring ceftazidime plus linezolid; 95% CI − 40.6, 8.2), as well as in	Thank you for highlighting the Bugos et al. (2019) study. This study is not a systematic review or an RCT so it does not meet the review protocol inclusion criteria for this guideline.

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					patients with any Gram-positive pathogen in the HAP study (− 11.5%, favouring ceftazidime plus linezolid; 95% CI − 24.2, 1.3). When analysed by causative pathogen type, patients with any *S. aureus* showed a higher proportion of patients with early improvement at Day 4 compared with the comparator treatment, suggesting an advantage with the rapid bactericidal action of ceftobiprole over other cephalosporins in high-risk patients with HAP (excluding VAP) The safety profile of the molecule reflected the class, whereby AEs, treatment related AEs and SAE for ceftobiprole and the comparator treatments were broadly similar, with some minor differences [Scheeren, et al. BMC Infect Dis 2019 ;19(1):195]. As the elderly population increases, a necessary consideration of the different physiological conditions and comorbid conditions associated to aging must be made. Among these, frailty features associated to neurological diseases, immune-compromised statuses and different metabolic states may imply that commonly sued drugs may not necessarily be adequately effective, or safe. Moreover, elderly and frail patients may be at higher risk of serious infections and colonisation by MDR organisms. As adequate rapid empirical therapy is recommended to improve its prognosis, a rational use of newer enhance-spectrum antibiotics may be considered in such populations. [Burgos J, et al. Expert Opin Pharmacother. 2019; 20 (4): 423-434].	
42	Correvio Ltd.	Guideline	4	Table 1	The NICE experts committee agrees on the choice of empirical therapy, and the use of broad-	Thank you for your comment. The committee discussed your comment and

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					spectrum agents. Nonetheless, we believe that the recommendations may imply there will be no place for molecules with activity on Gram-positive as well as on Gram-negative pathogens in a selected subgroup of patients. Risk-stratification is crucial to assess the correct use of molecules, whereby some patients may benefit from molecules with strong bactericidal activity on clinically relevant pathogens. In a recent surveillance study on respiratory-tract pathogens collected in the United Kingdom and Ireland during 2014–2015, ceftobiprole demonstrated potent *in vitro* activity against pathogens commonly associated with HAP: against all *S. aureus* isolates tested, including both MSSA and MRSA, including *S. aureus* isolates resistant to other antimicrobial agents, such as ciprofloxacin (18.5% resistant strains) and erythromycin (20.8% resistant strains). Only vancomycin demonstrated similar susceptibility rates against all *S. aureus* isolates, MSSA, MRSA, and *S. pneumoniae*, susceptibility rates versus ceftobiprole observed in this were 100%, 100%, and 99.8% respectively [Santerre-Henriksen A, et al., Infect Drug Res 2018;11:1309-1320]. Gram-negative bacteria associated with HAP also showed high susceptibility to ceftobiprole, with rates of 83.4% and 88.1% in *K. pneumoniae* and *E. coli* isolates, respectively. Of note, 86% of Pseudomonas aeruginosa (N=214) isolates were susceptible to ceftobiprole. This supports the use of ceftobiprole against infection caused by pathogens commonly associated with lower-respiratory tract infections	based on the evidence considered that the antibiotic choices outlined provide adequate coverage of gram-positive and gram-negative pathogens associated with hospital-acquired pneumonia. The committee referred to the recommendations which outline items to consider when choosing an antibiotic and feel that these address the concerns you raise regarding the selection of antibiotic for the treatment of hospital-acquired pneumonia in adults, young people and children and risk stratification. Further to this the prescribing tables have been amended and further stratify antibiotic choice based on hospital-acquired pneumonia onset and severity with additional emphasis placed on the role of specialist microbiological advice and local resistance data when making prescribing decisions for hospital-acquired pneumonia. Thank you for highlighting the Santerre-Henriksen et al (2018) study. This study is not a systematic review or an RCT and does not meet the review protocol inclusion criteria for this guideline. Ceftobiprole was a specified search term in the review protocol for this guideline. The evidence review identified Awad et al (2014) study (which the Scheeren et al. (2019) post-hoc analysis is derived from) with no significant difference identified between ceftobiprole and ceftazidime plus linezolid in people with non-ventilator-associated hospital-acquired pneumonia. The committee has discussed

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					[Santerre-Henriksen A, et al., Infect Drug Res 2018;11:1309-1320]. The bactericidal activity of the molecule should specifically be taken into account for the frail/elderly populations, who may benefit from a potent bactericidal molecule with an enhanced spectrum of activity (Gram-positive and Gram negatives) [Scheeren, et al. BMC Infect Dis 2019;19(1):195].	your comment and based on the evidence has not specifically recommended ceftobiprole. However, the prescribing table has been amended to include a list of options, with antibiotic choice being based on local resistance data and specialist microbiological advice only
43	Correvio Ltd.	Guideline	4	Table 1	We note that the choice of antibiotics offered in Table 1 may not exclude the development of potential *C. difficile* infections. [Slimings C J Antimicrob Chemother. 2014 ;69(4):881-91]. Agents with limited activity on *P. aeruginosa* may increase the risk of carbapenem-resistant *P. aeruginosa* colonization [Coppry J Antimicrob Chemother. 2019 Feb 1;74(2):503-510]. Coverage with antibiotics that have limited impact on the gut microflora (especially on anaerobes) and modest activity on *C. difficile* may be advisable in order to avoid unwanted colonisation [Murthy B, Schmitt-Hoffmann A. Clin Pharmacokinet 2008; 47:21-33; Nerandzic MM, Donskey CJ. Antimicrob Agents Chemother 2011; 55:2174–7; Bäckström T, et al. Int J Antimicrob Agents 2010; 36:537-41 Ednie L, Shapiro S, Appelbaum PC. Diagn Microbiol Infect Dis 2007; 58(1): 133–6]	Thank you for your comment and the references. The committee discussed your comment regarding *Clostridium difficile* infection and recommendations have been amended to make specific reference to the consideration of the risk of *Clostridium difficile* infection amongst other adverse effects when choosing broad spectrum antibiotics. Hospital-acquired pneumonia is a serious infection that requires effective treatment with a broad spectrum antibiotic, based on local resistance data and specialist microbiological advice. On review of the references outlined they are not systematic reviews or RCTs and do not meet the review protocol inclusion criteria for this guideline.
44	Correvio Ltd.	Guideline	4	Table 1	We believe that the above mentioned (comment 1) subgroups of patients may not always benefit from vancomycin therapy, as TDM may not always be available. In particular, patients at risk of developing renal failure or at risk of underdosing/overdosing may not benefit from	Thank you for your comment. The committee has discussed your comment and has added teicoplanin as an option (under specialist advice only) if MRSA is suspected or confirmed, to address concerns about people at risk of developing

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					such a choice (Mizokami et al, Clin Interv Aging 2013;8:1015-21] As the risk of toxicity and resistance-development may outnumber beneficial effects of the molecule. [Jeffres MN The Whole Price of Vancomycin: Toxicities, Troughs, and Time. Drugs. 2017 Jul;77(11):1143-1154] As suggested in the literature, a less toxic choice but with similar activity is available and would be more beneficial in such cohorts. [Santerre-Henriksen A, et al.; Infect Drug Res 2018;11:1309-1320]	renal failure and the availability of therapeutic drug monitoring.