# Managing Common Infections

## Pyelonephritis (acute): antimicrobial prescribing

08/05/2017 – 05/06/2018

| ID | ORGANISATION NAME | DOCUMENT | PAGE NO. | LINE NO. | COMMENTS<br>Please insert each new comment in a new row | DEVELOPER'S RESPONSE<br>Please respond to each comment |
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| 1 | British Infection Association | Guideline | 5 and 7 | Tables 1 and 3 | Ceftriaxone is suitable as outpatient parenteral antibiotic therapy only (not as inpatient treatment) – this needs to be stated | Thank you for your comment. The committee discussed your comment and did not agree that ceftriaxone is only suitable for outpatient parenteral antimicrobial therapy (OPAT) administration. Please note the guideline covers both primary and secondary care settings. It does not specify the care setting in which antibiotic choice is to be made in order to allow for services such as outpatient parenteral antimicrobial therapy (OPAT). |
| 2 | British Infection Association | Guideline | 5,6, and 7 | Table 1, 2 and 3 | Second choice intravenous antibiotic if "higher risk of developing resistance" – please state what criteria determine whether there is a higher risk of developing resistance | Thank you for your comment. The committee discussed your comment and the wording in the table was changed to 'Second choice intravenous antibiotics'. |
| 3 | British Infection Association | Guideline | 6 | Table 2 | First choice intravenous antibiotic (if vomiting, unable to take oral antibiotics, or severely unwell)- Cefuroxime<br>750 mg three or four times a day: this would be a suboptimal dose for a significant infection, our normal practice is to use 1.5g three times a day unless the patient's renal function necessitates a lower dose. | Thank you for your comment. The committee has discussed your comment and has made changes to Table 2 to include increased dosages for severe infection in line with the BNF. |
| 4 | British Infection Association | Guideline | 5,6, and 7 | Tables 1, 2 and 3 | First choice intravenous antibiotic (if vomiting, unable to take oral antibiotics or severely unwell). Antibiotics may be combined if sepsis a concern – the guidance needs to state that precise first choice stated in local antibiotic policies is ultimately determined by the local susceptibility patterns – same applies to table 2 and 3. | Thank you for your comment. The committee has discussed your comment and has amended recommendation 1.3.1 to state that account should be taken of local antimicrobial resistance data. |
| 5 | British Infection Association | Guideline | 5 | Table 1 | Why is cefuroxime not included as an IV option? It needs to be. | Thank you for your comment. The committee has discussed your comment and added cefuroxime as option for IV treatment. |
| 6 | British Infection Association | Guideline | 2 | Table 1 | Ciprofloxacin 400mg tds is not a routinely used dose in our clinical practice for pyelonephritis. This appears to be a suggestion for over-treatment unless there is a known Pseudomonas or organism with a high ciprofloxacin MIC. Whilst it might be appropriate after an MSU result, it is not appropriate as empirical treatment. | Thank you for your comment. The committee discussed your comment and agreed that there was sufficient trial evidence supporting the use of quinolones to justify the inclusion of either ciprofloxacin or levofloxacin. Ciprofloxacin was chosen as it has a narrower spectrum of activity than levofloxacin. The committee noted that use of broad-spectrum antibiotics, such as quinolones, can create a selective advantage for bacteria resistant to these second-line broad-spectrum agents, allowing such strains to proliferate and spread. And, by disrupting normal flora, broad-spectrum antibiotics can leave people susceptible to harmful bacteria such as Clostridium difficile infection in community settings. However, these antibiotics are appropriate for the empirical treatment of acute pyelonephritis, where coverage of more resistant strains of common bacterial pathogens is required. |

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| 7 | British Infection Association | Guideline | general | | The antibiotic choices make no reference to local resistance rates or for come choices national data (Nottinghamshire have high co-amoxiclav resistance rates as does the recent national E coli BSI dataset) plus advises high risk antibiotics for inpatient treatment from the C difficile point of view. The document seems to contradict our stewardship goals in these areas. | Thank you for your comment. The Committee has discussed your comment and has amended recommendation 1.3.1 to state that account should be taken of local antimicrobial resistance data. |
| 8 | Scottish Antimicrobial Prescribing Group (SAPG), Healthcare Improvement Scotland | Visual summary | General | General | Would be useful to have signs & symptoms for diagnosis in visual aide.<br>Gentamicin and amikacin dosage should refer to local guideline rather than just giving mg/kg<br>Gentamicin regimes differ across boards and dosing regimes are dependant on renal function. Dependant on therapeutic monitoring dosing frequency is variable as some patients may receive 36hrly or 48hrly doses. Confusing to state “daily”. By providing a blanket statement that all patients should receive 7mg/kg is a significant patient safety risk.<br>Amikacin dosing is also dependant on renal function and dependant on therapeutic monitoring to determine dosing frequency. | Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis. Providing further details on diagnostic signs and symptoms in the guideline is out of scope, but further background information on signs and symptoms is given in the evidence review.<br><br>The Committee has discussed your comment and has amended tables 1 and 3 to include information on dose adjustment according to serum concentration of gentamicin and amikacin. All doses are taken from the BNF. |
| 9 | Scottish Antimicrobial Prescribing Group (SAPG), Healthcare Improvement Scotland | Guideline | General | General | Would be helpful to have signs & symptoms of pyelonephritis at start of document.<br>Would be helpful to link to and refer to NEW2 to assist in identifying deteriorating patients.<br>Gentamicin regimes differ across boards and dosing regimes are dependant on renal function. Dependant on therapeutic monitoring dosing frequency is variable as some patients may receive 36hrly or 48hrly doses. Confusing to state “daily”. By providing a blanket statement that all patients should receive 7mg/kg is a significant patient safety risk.<br>Amikacin dosing is also dependant on renal function and dependant on therapeutic monitoring to determine dosing frequency. | Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis. Providing further details on diagnostic signs and symptoms, or the identification of deteriorating patients in the guideline is out of scope. Further background information on signs and symptoms is given in the evidence review.<br><br>The Committee has discussed your comment and has amended tables 1 and 3 to include footnotes on dose adjustment according to serum concentration of gentamicin and amikacin. All doses are taken from the BNF. |
| 10 | Scottish Antimicrobial Prescribing Group (SAPG), Healthcare Improvement Scotland | Guideline | 5 | Table 1 | Avoid levofloxacin as first choice antibiotic<br>Note that oral ciprofloxacin has very similar bioavailability to IV and therefore IV should only be used if the oral route is compromised.<br>It is not helpful to the clinician to have 5 choices as first line IV antibiotics. | Thank you for your comment. The committee discussed your comment and agreed that there was sufficient trial evidence supporting the use of quinolones to justify the inclusion of either ciprofloxacin or levofloxacin. Ciprofloxacin was chosen as it has a narrower spectrum of activity than levofloxacin.<br><br>Please note that IV antibiotics in the tables are for those unable to take oral antibiotics or those who are severely unwell.<br><br>The committee discussed your comment but as outlined in the rationale, agreed, based on experience, that several intravenous antibiotics should be available for people with acute pyelonephritis. This enables antibiotics to be selected based on antibiotic susceptibilities from culture results when available, local resistance patterns, risk of resistant bacteria, and known patient factors (such as whether the person has a higher risk of developing complications). In line with antimicrobial stewardship, narrower spectrum antibiotics should be used wherever possible. |

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| 11 | Scottish Antimicrobial Prescribing Group (SAPG), Healthcare Improvement Scotland | Guideline | 5-6 | Table 2 | Why choose cefalexin or cefuroxime over co-amoxiclav in pregnancy? | Thank you for your comment. The committee discussed your comment and, as outlined in the rationale, co-amoxiclav was not recommended because of high resistance levels nationally and the risks of treatment failure in pregnancy. Resistance to co-amoxiclav is currently 19.8% of *E. coli* isolates reported to PHE, whereas resistance of *E. coli* isolates to cefalexin is 9.9% of isolates in England. |
| 12 | Scottish Antimicrobial Prescribing Group (SAPG), Healthcare Improvement Scotland | Guideline | 6-7 | Table 3 | Gentamicin is subject to different dosage schedules and dosing intervals are dependent on the results of therapeutic drug monitoring. It is not helpful to the clinician to have 5 choices as first line IV antibiotics. | Thank you for your comment. The Committee has discussed your comment and has amended tables 1 and 3 to include information on dose adjustment according to serum concentration of gentamicin and amikacin.<br><br>The committee discussed your comment but as outlined in the rationale, agreed, based on experience, that several intravenous antibiotics should be available for people with acute pyelonephritis. This enables antibiotics to be selected based on antibiotic susceptibilities from culture results when available, local resistance patterns, risk of resistant bacteria, and known patient factors (such as whether the person has a higher risk of developing complications). In line with antimicrobial stewardship, narrower spectrum antibiotics should be used wherever possible. |
| 13 | Scottish Antimicrobial Prescribing Group (SAPG), Healthcare Improvement Scotland | Guideline | General | General | Each guideline refers to “Allergic reactions to penicillins occur in 1-10% of people and anaphylactic reactions occur in less than 0.05%. People with a history of atopic allergy (for example, asthma, eczema and hay fever) are at a higher risk of anaphylactic reactions to penicillins” This is at odds with the British Society of Allergy and Clinical Immunology (BSACI) guidelines (published in Clinical & Experimental Allergy 45;300-327). They state<br>“The prevalence of penicillin hypersensitivity in the general population is unknown as there are no prospective studies evaluation sensitisation rates during treatment”<br>“Atopy does not predispose to the development of allergic reactions to penicillin, but asthma can be a risk factor for life threatening reactions” | Thank you for your comment. NICE has amended the section on penicillin allergy to reflect the advice given in the NICE guideline on drug allergy. |
| 14 | National Minor Illness Centre | Visual summary<br><br>Guideline | 1<br><br>3 | Top white box<br><br>9 | The recommendation to advise of “possible adverse effects of antibiotics include diarrhoea and nausea” may not be appropriate to this particular guideline for upper urinary tract infection. Pyelonephritis is a more serious infection than lower UTI. General malaise, fever and disturbance of gut function may be as a result of the condition rather than the antibiotic. There is a greater need for effective treatment. There could be a danger that if the patient is warned about these symptoms being a result of taking the antibiotic prescribed, that they might stop the treatment inappropriately. The second section of advice to the patient covers what the patient should do if they develop significant new symptoms. Then the clinician can decide if switching the antibiotic is necessary. | Thank you for your comment. The Committee agreed people with acute pyelonephritis should be told of the common side effects associated with antibiotic treatment. This is an essential part of professional practice for prescribers (For example see the General Medical Councils Good practice in prescribing and managing medicines and devices, part 24). However the wording of recommendation 1.1.8 has been amended to ‘When an antibiotic is given, as well as the general advice on self-care, give advice about: possible adverse effects of the antibiotic, particularly diarrhoea and nausea (although nausea with vomiting can also be caused by pyelonephritis, indicating worsening symptoms).<br><br>It is expected (and covered in the guideline, see Table 1, 2 and 3) that if a person is vomiting or unable to take oral antibiotics at the time they are |

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| | | | | | | seen then parenteral antibiotics would be appropriate. If vomiting was a new symptom during oral treatment then recommendation 1.1.8 advises that they should seek medical help. |
| 15 | National Minor Illness Centre | Visual summary<br><br>Guideline | 2<br><br>3<br><br>5, 6 | Left box<br><br>6<br><br>11, 22 | The dose of Co-amoxiclav is not as it appears in the BNF: “Prescribing and dispensing information<br>Doses are expressed as co-amoxiclav: a mixture of amoxicillin (as the trihydrate or as the sodium salt) and clavulanic acid (as potassium clavulanate); the proportions are expressed in the form x/y where x and y are the strengths in milligrams of amoxicillin and clavulanic acid respectively.”<br>In contrast, the suspensions are given in the BNF format. | Thank you for your comment. The Committee has discussed your comment and has amended table 1 to state 500/125 mg |
| 16 | National Minor Illness Centre | Visual summary<br><br>Guideline | 2<br><br>6 | Right box<br><br>2 | There is a lack of evidence on appropriate dose and duration of antibiotics for this condition. Cefalexin is the first choice antibiotic for pregnant women aged 12 years and over. The dose is recommended as 500mg twice or three times a day. Is 500mg twice daily adequate to treat pyelonephritis, especially as in pregnancy there are additional risks from the infection and some impairment of the immune response? Even for non-pregnant young people aged 12-17 the BNFC recommends a standard dose of ‘500 mg 2–3 times a day’ and for ‘Serious susceptible infections due to sensitive Gram-positive and Gram-negative bacteria - For Child 12–17 years 1–1.5 g 3–4 times a day.’ | Thank you for your comment. The committee has discussed your comment and amended the dose of cefalexin in the guideline to include increased dosages for severe infection in line with the BNF. |
| 17 | National Minor Illness Centre | Visual summary | 3 | 6 | It would be clearer to give the dose per kg first and only state the concentration of the medicine once. When a dose per kg is given in the BNFC, calculating a dose for a child by weight is usually preferable to using a standard dose for an age range as it should give a more appropriate dose for the individual, so long as they are not extremely obese. In view of this, it would be better to state the dose per kg first.<br>For example,<br>‘6 to 11 years, 5 ml of 250/62 suspension or 0.15 ml/kg of 250/62 suspension three times a day for 7 to 10 days (dose doubled in severe infection)’<br>would become:<br>‘6 to 11 years, 0.15 ml/kg or 5 ml of 250/62 suspension three times a day for 7 to 10 days (dose doubled in severe infection)’ | Thank you for your comment. The committee has discussed your comment and amended the tables to give dose per kg first. |
| 18 | National Minor Illness Centre | Visual summary | 3 | 10 | To be consistent and clearer, it might be better to use the dose schedule of Cefalexin for children as it appears in the visual summary for lower UTI. In this pyelonephritis visual summary the dose per kg appears after the set dose for the age range, whereas it is the other way around for trimethoprim in the same table and in the lower UTI guideline. | Thank you for your comment. The committee has discussed your comment and amended the tables to give dose per kg first. |
| 19 | National Minor Illness Centre | Visual summary | 3 | 18 | The dose ranges for Ceftriaxone could be combined for 9 to 16 years. | Thank you for your comment. The committee has discussed your comment but the wording was not amended, because of the different weight instructions:<br>3 months to 11 years (up to 50 kg), 50 to 80 mg/kg once a day (maximum 4 g per day)<br>9 to 11 years (50 kg and above), 1 to 2 g once a day<br>12 to 15 years, 1 to 2 g once a day |
| 20 | British Association of Urological Surgeons (BAUS) | Guideline | General | General | No mention of the role of imaging is made in the guideline. | Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, therefore imaging is out of scope. |
| 22 | Eumedica SA | Guidelines | 5 | Table 1 | The committee highlighted that the most common causative pathogens in acute pyelonephritis are Gram-negative bacteria among which *E. coli*, *P. mirabilis* and *Klebsiella* accounted for up to 95% of the causative bacteria. In addition, the committee pointed out that use of broad-spectrum antibiotics, such as co-amoxiclav, cephalosporins or quinolones, can create a selective advantage for bacteria resistant | Thank you for your comment. While NICE appreciates that temocillin is a useful antibiotic in treating infection, unfortunately we found no evidence from randomised controlled trials that evaluated temocillin in people with acute |

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| | | | | | to these broad-spectrum agents, allowing such strains to proliferate and spread. And, by disrupting normal flora, broad-spectrum antibiotics can leave people susceptible to harmful bacteria such as Clostridium difficile infection in community settings.<br>We would like to emphasize on the usefulness of temocillin as an alternative to the use of these broad-spectrum antibiotics as it could be seen as a first choice intravenous antibiotic:<br>- Temocillin is mainly active against the Enterobacterales, the most frequent bacteria seen in acute pyelonephritis (up to 95%, as pointed out by the committee).<br>- Temocillin is not active against pathogens such as Pseudomonas, Gram-positive or anaerobes but these pathogens only accounted for a fraction of bacteria found in acute pyelonephritis. In high risk patients, these bacteria can be covered by the addition of an aminoglycoside.<br>- The narrow spectrum activity of temocillin makes that<br>o The drug has not been associated with a selective pressure on resistant bacteria<br>o It has few impact on the intestinal microbiota (Mittermayer HM Drugs. 1985;29 Suppl 5:43-8) and,<br>o The risk of inducing gastrointestinal events is lower than with other drugs (Boon RJ and Beale AS Antimicrob Agents Chemother. 1985 Jun;27(6):980-1; Habayeb H et al. Eur J Clin Microbiol Infect Dis. 2015 Aug;34(8):1693-9)<br>- The clinical efficacy of temocillin is unaffected by the presence of ESBL or AmpC-producing strains (Balakrishnan I et al J Antimicrob Chemother. 2011 Nov;66(11):2628-31). A recent study estimated the prevalence of colonization with CTX-M ESBL-producing Enterobacteriaceae in England at 7.3% (McNulty CAM et al, J Antimicrob Chemother. 2018 Mar 5. doi: 10.1093/jac/dky007). Knowing that ESBL infections are associated with an increased risk of morbidity, mortality and cost (WHO report), it is important that the first-line treatment is also active against these resistant pathogens. This will not be necessarily the case the most of the suggested IV drugs included in the document.<br>- Temocillin is used since the 80's in Belgium and no increase of resistance has been shown so far, despite a broader use. The most recent data still report very high susceptibility level of Enterobacteriaceae to temocillin (Rodriguez-Villalobos H, J Antimicrob Chemother. 2011 Jan;66(1):37-47). No difference of MIC90 is observed between these data and those initially included in the registration file. The Belgian Antibiotic Policy Coordination Committee recently published the national guidelines for the treatment of infection in the secondary care setting. This was elaborated by the national society of infectious diseases (SBIMC). In these guidelines, temocillin is recommended as long as with other options for the empirical treatment of acute complicated pyelonephritis (alone or in combination with an aminoglycoside in case of sepsis or septic choc; page 309), catheter-associated UTI (in combination with an aminoglycoside; page 313), UTI in patient with polycystic kidney disease (in combination with a quinolone or co-trimoxazole; page 314) and, urinary tract infections in pregnant woman (alone or in combination with an aminoglycoside in case of sepsis or septic choc; page 316).<br><br>There is a chain of reaction when looking at the use of antibiotics and their resistance: Increased use of fluoroquinolones or third-generation cephalosporins → selective pressure for ESBL → increased use of carbapenems → selective pressure for CPE → increased use of colistin → selective pressure for mcr1 → … leading to the apocalyptic scenario depicted by Jim O'Neill report. | pyelonephritis. Temocillin was specifically included by name in the NICE search strategy. In relation to the submitted articles:<br>• Mittermayer (1985) did not meet the criteria for inclusion as it was in healthy volunteers and falls outside the date range set by the committee for includable studies (before 2006)<br>• Boon and Beale (1985) did not meet the criteria for inclusion as it was conducted in animals (hamsters) not humans and falls outside the date range set by the committee for includable studies (before 2006)<br>• Habayeb et al. (2015) did not meet the criteria for inclusion as it was in people with severe hospital-acquired pneumonia and was a retrospective audit not a randomised controlled trial<br>• Balakrishnan et al. (2011) did not meet the criteria for inclusion as it was a retrospective data analysis not a randomised controlled trial, it is unclear whether those people with a urinary tract infection in this study had acute pyelonephritis (unclear population)<br>• Hawkey et al. (2018) cited in the comment as McNulty et al. (2018) did not meet the criteria for inclusion as it is not an intervention study and was published after the guideline searches were conducted, however, the committee are aware of the paper as one of the authors is a member of the standing committee for common infections<br>• World Health Organisation (2014) please note that NICE uses UK data on extended-spectrum beta-lactamases (ESBL) available through the ESPAUR report as resistance can vary between countries<br>• Rodriguez-Vilalobos et al. (2011) did not meet the criteria for inclusion as it was a data study not a randomised controlled trial, it is unclear whether those people providing urinary samples in this study had acute pyelonephritis (unclear population)<br>• Belgian Antibiotic Policy Coordination Committee (2017) guidelines do not meet the criteria for inclusion as they are not randomised controlled trials or systematic reviews and are not available in English (language)<br><br>The O'Neill reports (2014 and 2016) are major drivers for the NICE guidelines on common infections (please see the final scope document). |

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| | | | | | Because of this, it is important to spare the use of colistin, of carbapenems but also of cephalosporins and fluoroquinolones whenever possible. To this end, the use of temocillin should be considered for the empirical treatment of infections where the likelihood of susceptible bacteria is high, which is the case of acute pyelonephritis. We are therefore asking the committee to review their position and include temocillin in the guidelines. As highlighted by the review on antimicrobial resistance chaired by Jim O'Neill, the cost of dealing with resistance is far smaller than not taking action. | |
| 23 | The British Society for Antimicrobial Chemotherapy | Guideline | 5 | 1.3.2 | It would be useful to guide the user to which patients might benefit from IV antibiotics. i.e. which parameters would put the patient in a severe infection category. | Thank you for your comment. Unfortunately prognostic studies are outside the scope of this guideline. It is anticipated that prescribers will use clinical judgement and experience to determine who will benefit from IV therapy. |
| 24 | The British Society for Antimicrobial Chemotherapy | Guideline | 5 | 1.3.3 | Table 1 lists co-amoxiclav first line orally and IV. Locally our co-amoxiclav resistance in urinary and blood E.coli isolates is >50% and I believe that to be the same nationally which would make co-amoxiclav unsuitable for empiric therapy. Trimethoprim is listed with the caveat if organism susceptible, I think that should be the same for co-amoxiclav. | Thank you for your comment. The committee discussed your comment and have amended the antibiotic table to recommend co-amoxiclav (only if culture results available and susceptible). |
| 25 | The British Society for Antimicrobial Chemotherapy | Guideline | General | General | General concern is the antibiotic choices make no reference to local resistance rates or for come choices national data (we have a high co-amoxiclav resistance rates as does the recent national E coli BSI dataset) plus advises high risk antibiotics for inpatient treatment from the C difficile point of view | Thank you for your comment. The committee has discussed your comment and has amended recommendation 1.3.1 to state that account should be taken of local antimicrobial resistance data. The antibiotic table has also been amended to recommend co-amoxiclav (only if culture results available and susceptible).<br><br>The committee noted that use of broad-spectrum antibiotics, such as cephalosporins, quinolones and co-amoxiclav, can create a selective advantage for bacteria resistant to these second-line broad-spectrum agents, allowing such strains to proliferate and spread. And, by disrupting normal flora, broad-spectrum antibiotics can leave people susceptible to harmful bacteria such as Clostridium difficile infection in community settings. However, these antibiotics are appropriate for the empirical treatment of acute pyelonephritis, where coverage of more resistant strains of common bacterial pathogens is required. |
| 26 | The British Society for Antimicrobial Chemotherapy | Guideline | General | General | We are concerned about the mention of levofloxacin as a first choice antibiotic, as we have moved away from the quinolones. | Thank you for your comment. The committee discussed your comment and agreed that there was sufficient trial evidence supporting the use of quinolones to justify the inclusion of either ciprofloxacin or levofloxacin. Ciprofloxacin was chosen as it has a narrower spectrum of activity than levofloxacin. |
| 27 | The British Society for Antimicrobial Chemotherapy | Guideline | General | General | There is no choice offered for an antibiotic in pregnant patients who have a history of an anaphylactic reaction to penicillin. | Thank you for your comment. The committee discussed your comment and recommended that a local microbiologist should be consulted for second choice antibiotics (including in penicillin allergy). |
| 28 | Royal College of Pathologists | Guideline | general | general | All five guidelines have insufficient discussion on the diagnosis of urinary tract infections. All five guidelines start with an assumption that a correct clinical diagnosis of UTI has been made. In practice, this aspect of UTI management is probably the most problematic. | Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, and further information on diagnosis is out of scope. The guidelines start from the point that a diagnosis has been made. |

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| 29 | Royal College of Pathologists | Guideline | 2 | 1.1.3, 1.1.4, 1.1.5 | Pyelonephritis is a serious infection that can readily progress to life-threatening sepsis. Consequently, it is inappropriate for this infection to be managed in primary care. At the very least, patients should be referred to an emergency department for initial management and this must include collection of blood cultures as well as urine for microbiological investigations. | Thank you for your comment. The Committee reviewed the evidence from the randomised controlled trials (See the summary of included studies in the evidence review) which demonstrated that in many cases acute pyelonephritis can be safely managed in primary care. The Committee (in recommendations 1.1.10; 1.1.11 and 1.1.12) set out when referral to hospital is indicated. |
| 30 | Royal College of Pathologists | Guideline | 2 | 1.1.6 | The enteral route may not be a secure route for antibiotic administration in patients with pyelonephritis and intravenous treatment may be necessary. | Thank you for your comment. The Committee has made recommendations on when parenteral antibiotics should be considered (see Tables 1, 2 and 3 for details). |
| 31 | Royal College of Pathologists | Guideline | 5 | Table 1, Table 2, Table 3. | The recommendation of co-amoxiclav as empirical first choice treatment is likely to have a high failure rate in areas of the UK where co-amoxiclav resistance is frequent. There should be advice to follow local prescribing guidance for the choice of agent in these tables.<br>The gentamicin and amikacin entries should carry the caveat that therapeutic drug monitoring is required.<br>The entry, “Second choice intravenous antibiotic if higher risk of developing resistance”, seems to imply a concern that the patient might develop infection with a resistant organism during treatment. This is very unlikely. This may be more appropriately phrased as, “Second choice intravenous antibiotic if higher risk of infection with resistant organism”. | Thank you for your comment. The Committee has discussed your comment and has amended recommendation 1.3.1 to state that account should be taken of local antimicrobial resistance data. The antibiotic table has also been amended to recommend co-amoxiclav (only if culture results available and susceptible).<br><br>The Committee has discussed your comment and has amended tables 1 and 3 to include information on dose adjustment according to serum concentration of gentamicin and amikacin.<br><br>The committee discussed your comment and the wording in the table was changed to ‘Second choice intravenous antibiotics’. |
| 32 | UK Clinical Pharmacy Association | Visual summary | General | General | Background should come before treatment advice | Thank you for your comment. Document format of the visual summary will be considered by the NICE editorial team. |
| 33 | UK Clinical Pharmacy Association | Visual summary | General | General | The following statement should be included within the flow chart before offering an antibiotic rather than in a box at the end<br><br>When prescribing antibiotics, take account of severity of symptoms, risk of complications, previous urine culture and susceptibility results, previous antibiotic use which may<br>have led to resistant bacteria | Thank you for your comment. Document format of the visual summary will be considered by the NICE editorial team. |
| 34 | UK Clinical Pharmacy Association | Visual summary | General | General | Needs a statement on what to do if higher risk of a resistant case (e.g. ESBL) – D/W Microbiologist and consider admission or OPAT | Thank you for your comment. The visual summary states ‘When results of urine culture available:<br>• review the choice of antibiotic, and<br>• change antibiotic according to susceptibility results if bacteria are<br>resistant, using narrow spectrum antibiotics when possible<br><br>A review and change in antimicrobial therapy according to susceptibility results would include cases of resistance. |
| 35 | UK Clinical Pharmacy Association | General | General | General | Since co-amoxiclav has a wide therapeutic range in practice it is preferable to use the dose banding rather than the ml/kg dosing in most cases even if children are considered small for their age, this allows for ease of administration and improves adherence. We need to try to avoid unnecessarily complex dosing such as 2.6ml. | Thank you for your comment. NICE uses the BNFC for dosages in children when making recommendations, where both dose per kg and dose bands are given. |

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| 36 | UK Clinical Pharmacy Association | General | General | General | Usual dosing for cefotaxime in > 3 months is 50mg/kg 6-8hourly rather than 12hourly. | Thank you for your comment. The Committee agreed following further discussion about antibiotic choice and rationalising different cephalosporins across the suite of UTI guidelines that cefuroxime was a more suitable choice (due to being available orally as well as intravenously) than cefotaxime; and cefotaxime was removed. |
| 37 | UK Clinical Pharmacy Association | General | General | General | Ceftriaxone dosing – although the BNF-C states to dose as per adults in children 9-11 years (50kg and above) and over 12 years – in practice many paediatric centres often continue to prescribe on a mg/kg basis with a max dose of 4g/day. | Thank you for your comment. NICE uses the BNFC for dosages in children when making recommendations. |
| 38 | UK Clinical Pharmacy Association | General | General | General | Should maximum doses be added for aminoglycosides as per other antibiotics? | Thank you for your comment. The Committee had discussed your comment and amended Table 1 with maximum doses for aminoglycosides where stated in the BNF. |
| 39 | UK Clinical Pharmacy Association | Visual Summary | General | General | Helpful to add information on diagnosis of pyelonephritis to the visual summary and how to differentiate from a lower UTI. | Thank you for your comment. The remit of this guidance is the management of common infections not diagnosis, and further information on diagnosis is out of scope. |
| 40 | UK Clinical Pharmacy Association | Evidence Summary | 18 | 33 | Ampicillin 10g three times a day should read 1g three times a day | Thank you for your comment. NICE has checked the reported dose and it is correct. The systematic review by Eliakim-Raz et al. (2013) Table 1 reports the dose in the study by Ode (1980) as Ampicillin 10 g X 3, we have checked the original study abstract online which states 'one group was given ampicillin in a daily dose of 30 g for three days'. |
| 41 | UK Clinical Pharmacy Association | Evidence Summary | 26 | 20 | Allergic reactions to penicillins (such as phenoxymethylpenicillin) occur in 1 to 10% of 20<br>treated people and anaphylactic reactions occur in less than 0.05% (BNF April 2018). Please use a more up-to-date, evidence based statement. Penicillin allergy is reported in this number of patients, but is commonly not reflective of a true allergy. The overdiagnosis/labelling of patients as pencillin allergic is a huge challenge for antibiotic stewardship therefore NICE guidance should accurately reflect this. | Thank you for your comment. NICE has amended the section on penicillin allergy to reflect the advice given in the NICE guideline on drug allergy. |
| 42 | Royal College of General Practitioners | Visual summary | 1 | | The 3-page visual summary of the recommendations, including tables to support prescribing decisions was not available to review | Thank you for your comment. NICE has not received any other instances of stakeholders being unable to access the visual summary, we apologise for any inconvenience. |
| 43 | Royal College of General Practitioners | General | 4 | | The guidance from Public Health England 2017 for primary care is slightly different and considers ESBL risk<br><br>https://bit.ly/2JclAkv<br><br>*If admission not needed, send MSU for culture and susceptibility testing, and start antibiotics.*<br>*If no response within 24 hours, seek advice.*<br>*If Extended Spectrum Beta-Lactamases ESBL risk, and on advice from a microbiologist, consider IV antibiotic via OPAT.* | Thank you for your comment. NICE is aware of the important role played by both Public Health England guidance on the treatment of acute pyelonephritis. We have worked closely with Public Health England to produce this guideline and the NICE antimicrobial prescribing guidelines will replace the PHE guidance as they are published. |
| 44 | Royal College of General Practitioners | Guideline | 4 | 1.2.2 | Could there be more specific advice re adequate fluid intake | Thank you for your comment. The committee have reworded recommendation 1.2.2 to state 'Advise people with acute pyelonephritis about drinking enough fluids to avoid dehydration'. |
| 45 | Royal College of General Practitioners | Evidence Review | 15 | | There is a new systematic review and meta-analysis comparing short versus long course antibiotic therapy for acute pyelonephritis in adults.<br>http://italjmed.org/index.php/ijm/article/view/itjm.2018.840 | Thank you for your comment. The study has been included following consultation. but as it offered no new evidence to that already included in the evidence review, and has very similar outcomes to |

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| | | | | | | the systematic review by Kyriakidou et al. 2008, it has been deprioritised by the Committee. |
| 46 | Nordic Pharma | Guideline | General | | As a general comment across all of the UTI guidelines, where fosfomycin is mentioned, please ensure it is very clear whether the guidelines are referring to IV or oral fosfomycin as these are both very different treatment options.<br>This distinction is often not made and can cause potential confusion e.g. the recent publication<br>Hawkey P. et al. J Antimicrob Chemother 2018; 73 Suppl 3: iii2–iii78 | Thank you for your comment. Please note that the tables within the guideline specify whether the antibiotic is first or second choice and whether they are oral or intravenous. |
| 47 | Nordic Pharma | Guideline | General | | With the recent publication of the white paper on the antibiotic supply chain by the Access to Medicine Foundation (available here) it is worth noting that since the introduction of licensed IV fosfomycin to the UK in 2014, consistent supply has been maintained, with two European manufacturing sites for security. | Thank you for your comment. |
| 48 | Nordic Pharma | Guideline | 10 | | In relation to 'People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta-lactam antibiotics (BNF, April 2018).'-<br>• Consideration should be given to include IV fosfomycin as it as the fosfomycin disodium molecule does not contain a beta lactam ring<br>• Due to a unique mode of action no cross-resistance and no cross-allergy has been observed during IV fosfomycin therapy. Refs:<br>○ Fomicyt IV (fosfomycin) Summary Of Product Characteristics July 2015<br>Rosales et al., [167]; Durupt et al., [50] | Thank you for your comment. While NICE appreciates that fosfomycin is a useful antibiotic in treating infection, unfortunately we found no evidence from randomised controlled trials that evaluated fosfomycin in people with acute pyelonephritis, and fosfomycin was specifically included by name in the NICE search strategy (see the evidence review document). |
| 49 | Nordic Pharma | Guideline | 5 | | Within table 1: there is evidence to support IV fosfomycin as a first line intravenous antibiotic:<br>• There is evidence to show the efficacy of IV fosfomycin in patients with pyelonephritis:<br>○ Zeus data: ID week 2017, poster #1845<br>○ Dinh A et all, Scand J Infect Dis 2012 Mar 44(3):182-189<br>○ Naber KG & Timmler R. Therapiewoche 1983;33:3300-3306.<br>○ Peters H.J. et al, MMW Munch Med Wochenschr. 1981 May 1;123 (18), 748-50<br>• IV fosfomycin achieves high renal tissue levels. It also reduces aminoglycoside-induced nephrotoxicity and has a nephro-protective effect, refs:<br>○ Inouye S, Niizato T, Komiya I, Yuda Y, Yamada Y. Mode of protective action of fosfomycin against dibekacin-induced nephrotoxicity in the dehydrated ratsJ Pharmacobiodyn. 1982 Dec;5(12):941-50<br>○ MacLeod et al , Journal of Antimicrobial Chemotherapy (2009) 64, 829–836<br>• If combination therapy is advised then suggest IV fosfomycin as a useful combination partner and avoiding combining two aminoglycosides due to nephrotoxicity – particularly in patients with renal impairment<br><br>• Fosfomycin therapy is not restricted by age – it is licensed for treating infections in adults (not excluding including pregnant women) and children – including neonates | Thank you for your comment. While NICE appreciates that fosfomycin is a useful antibiotic in treating infection, unfortunately we found no evidence from randomised controlled trials that evaluated fosfomycin in people with acute pyelonephritis, and fosfomycin was specifically included by name in the NICE search strategy (see the evidence review document). In relation to the submitted articles:<br>• Zeus data (2017) did not meet the criteria for inclusion as it is a conference abstract<br>• Dinh et al. (2012) did not meet the criteria for inclusion as it is a prospective cohort study not a systematic review or randomised controlled trial<br>• Naber & Timmler (1983) did not meet the criteria for inclusion as it falls outside the date range set by the committee for includable studies (before 2006) and is not available in English (language)<br>• Peters et al. (1981) did not meet the criteria for inclusion as falls outside the date range set by the committee for includable studies (before 2006) and is not available in English (language)<br>• Inouye et al. (1982) did not meet the criteria for inclusion as it is an animal study (rats) and falls outside the date range set by the committee for includable studies (before 2006)<br>• Macleod et al. (2009) did not meet the criteria for inclusion as it is not a randomised controlled trial or systematic review and was not in an acute pyelonephritis population (study in vitro and in vivo of against cystic fibrosis (CF) and non-CF bronchiectasis pathogens) |

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| 50 | Nordic Pharma | Guideline | 11 | | The reference to fosfomycin appears to be specific to oral fosfomycin as there is good renal tissue penetration with IV fosfomycin: *'Antibiotics that don't achieve adequate renal tissue levels, such as nitrofurantoin, **fosfomycin** and pivmecilinam, are avoided'*<br>• IV fosfomycin achieves high renal tissue concentrations due to it being metabolised by the kidneys<br>• IV fosfomycin is widely atoxic and may be given in large doses, irrespective of kidney function<br>  ○ Ref: Nissen LR et al. Infection 1986; 14(5): 246-250<br>Please note, comment 1 above re nephroprotective properties | Thank you for your comment. While NICE appreciates that fosfomycin is a useful antibiotic in treating infection, unfortunately we found no evidence from randomised controlled trials that evaluated fosfomycin in people with acute pyelonephritis, and fosfomycin was specifically included by name in the NICE search strategy. In relation to the submitted articles:<br>• Nissen et al. (1984) did not meet the criteria for inclusion as it is in people with pneumonia not acute pyelonephritis and it falls outside the date range set by the committee for includable studies (before 2006) |
| 51 | Healthcare Infection Society | guideline | general | general | What is the evidence that 14 days is required for trimethoprim treatment? This is not a distinction commonly used in clinical practice. | Thank you for your comment. Based on evidence (see sections 3.3.4 and 3.4.5 of the evidence review), resistance data (see section 5 of the evidence review) and their experience the committee agreed that, for oral treatment, a 14-day course of trimethoprim was required. There was no evidence for duration of treatment with trimethoprim shorter than 14 days. |
| 52 | Healthcare Infection Society | guideline | general | general | Why is levofloxacin included as a first line treatment? This is not standard UK practice and more expensive than ciprofloxacin. The additional Gram-positive cover is unnecessary if the predominant infecting organisms are Gram negative (and clearly unnecessary if ciprofloxacin is given as an option).<br>And if you include levofloxacin, why not ofloxacin? | Thank you for your comment. The committee discussed your comment and agreed that there was sufficient trial evidence supporting the use of quinolones to justify the inclusion of either ciprofloxacin or levofloxacin. Ciprofloxacin was chosen as it has a narrower spectrum of activity than levofloxacin. No evidence was found for ofloxacin in acute pyelonephritis. |
| 53 | Healthcare Infection Society | guideline | general | general | Total course length should be made more explicit where initial therapy is iv (rather than in a footnote). | Thank you for your comment. Document format will be considered by the NICE editorial team. |
| 54 | Healthcare Infection Society | guideline | general | general | In adults, 7 days may not be sufficient in severe infection and an option to extend to 10 days should be given. | Thank you for your comment. The recommendations are based on the evidence on course length from 2 systematic reviews which was considered by the Committee. The committee agreed that the shortest course that is likely to be effective should be prescribed to reduce the risk of antimicrobial resistance and minimise the risk of adverse effects. Based on evidence, they agreed that a short course of antibiotics (7 days or less, or 7 to 14 days) was generally as effective as a long course (10 days, or 14 to 42 days) of antibiotics for acute pyelonephritis. And agreed, based on this evidence, experience and resistance data that, for oral treatment, a 7-day course of all the recommended antibiotics was required to treat acute pyelonephritis in adults, apart from trimethoprim where 14 days was required. |