National Institute for Health and Care Excellence

Acute pyelonephritis and complicated urinary tract infection: antimicrobial prescribing guideline

Evidence review

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ISBN:

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1 Context

1.1 Background

Urinary tract infection (UTI) is a non-specific term that refers to infection anywhere in the urinary tract (Frassetto 2015). This evidence review covers acute pyelonephritis and complicated urinary tract infection. Uncomplicated lower UTI, recurrent UTI and catheter-associated UTI are covered in separate evidence reviews.

Pyelonephritis is an infection of the kidneys. Acute pyelonephritis may be caused by bacteria moving from the lower urinary tract or spreading via the bloodstream to the kidney. Most episodes of pyelonephritis are uncomplicated and result in no residual kidney damage. Complicated infections can result from underlying medical problems, genitourinary anatomical abnormalities, obstruction or multi-drug resistant pathogens (Frassetto 2015). Common signs and symptoms of pyelonephritis include acute-onset fever, chills, severe back or flank pain, nausea and vomiting, and costovertebral angle tenderness. The clinical knowledge summary (CKS) on pyelonephritis states that there are no clinical features or routine investigations that conclusively distinguish acute pyelonephritis from cystitis (lower UTI).

A complicated UTI is an infection associated with a condition (for example, a structural or functional abnormality of the genitourinary tract) or an underlying disease, which increases the risk of a more serious outcome or treatment failure (European Association of Urology [EAU] 2017). Factors associated with complicated urinary tract infections include indwelling urinary catheters, urinary obstruction, anatomical abnormalities and peri-operative and post-operative UTI. Urosepsis can occur when there is a systemic response to infection originating from the urinary tract and/or male genital organs. Urosepsis is accompanied by signs of systemic inflammation, presence of symptoms of organ dysfunction and persistent hypotension associated with tissue anoxia (EAU 2017).

A broad range of bacteria can cause a complicated UTI. The spectrum is much larger than in uncomplicated urinary tract infections, and bacteria are more likely to be resistant to antimicrobials, especially in a treatment-related complicated UTI (EAU 2017). Gram-negative bacteria are the predominant pathogens, with *Escherichia coli (E coli)* being the most common, particularly if the UTI is a first infection (EAU 2015). In complicated UTI the bacterial spectrum may vary over time and from one hospital to another (EAU 2017).

Laboratory urine culture is the recommended method to determine the presence of clinically significant bacteriuria in people suspected of having a complicated UTI (EAU 2017). Antimicrobial therapy for complicated UTI depends on the severity of illness at presentation as well as local resistance patterns. Urine culture and susceptibility testing should be performed, and initial empirical therapy should be tailored and followed by administration of an appropriate antimicrobial agent on the basis of the isolated pathogen (EAU 2017).

The NICE guideline on urinary tract infection in under 16s makes recommendations on the diagnosis of UTI in infants and children, including the use of imaging. The guideline recommends:

- infants and children who have bacteriuria and fever of 38°C or higher should be considered to have acute pyelonephritis/upper UTI
- infants and children presenting with fever lower than 38°C with loin pain/tenderness and bacteriuria should also be considered to have acute pyelonephritis/upper UTI
- all other infants and children who have bacteriuria but no systemic symptoms or signs should be considered to have cystitis/lower UTI.

Gram-negative bacteria are the most common causative pathogens in acute pyelonephritis, with *E. coli* causing 60% to 80% of uncomplicated infections. Other gram-negative pathogens include *Proteus mirabilis* (responsible for about 15% of infections) as well as Klebsiella (approximately 20%), Enterobacter, and Pseudomonas species. Less commonly, gram-positive bacteria such as *Enterococcus faecalis*, *Staphylococcus saprophyticus*, and *Staphylococcus aureus* may be seen.

Seven randomised controlled trials (RCTs) and 1 systematic review provided data about causative organisms in acute pyelonephritis and complicated UTI in adults in this evidence review (see Clinical effectiveness). No data on causative organisms of acute pyelonephritis or complicated UTI were found for children. *Escherichia coli* (*E. coli*) was the main causative organism in most studies although rates varied from 31.4% to 94.3%. The data are limited by variation in diagnosis (acute obstructive pyelonephritis, acute pyelonephritis and complicated UTI) and no or low growth of organisms in some studies which may explain some of the variation.

Two RCTs (Pasiechnikov et al. 2015 and Ren et al. 2017) reported that while *E. coli* was the main causative organism in the study the proportion with this organism were low (31.4% and 37% of isolates respectively). It should be noted that the study by Pasiechnikov et al. (2015) was in adults with acute obstructive pyelonephritis and supplementary data from the study by Ren et al. (2017) suggests no growth leading to no detectable pathogens in urine samples may have been an issue. In 1 systematic review (Kyriakidou et al. 2008) and 5 RCTs (Wagenlehner et al. 2015, Moramezi et al. 2008, Park et al. 2012, Talan et al. 2000 and Vazquez et al. 2012) *E. coli* was the main causative organism of acute pyelonephritis or complicated UTI accounting for between 73.5% to 94.3% of isolates. Other commonly reported pathogens (although not reported in all studies) included *Klebsiella spp*. (1.5% to 9%), *Pseudomonas aeruginosa* (2.9% to 17.9%), *Proteus spp*. (3.0% to 9.2%), *Staphylococcus spp*. and *Enterobacter spp*. were also commonly reported but at lower rates.

1.2 Managing infections that require antibiotics

Acute pyelonephritis is a bacterial infection needing treatment with an antibiotic that reaches therapeutic concentrations in the kidney. However, antibiotics should only be started when there is clear evidence of infection. In some instances the condition of the patient may necessitate prompt effective antibiotic treatment within 1 hour of diagnosis (or as soon as possible) in patients who have sepsis or life threatening infection, in these patients therapy should not be delayed but urine and/or blood samples for culture should, if possible, be obtained prior to treatment.

In line with the Department of Health guidance (Start Smart Then Focus) and the NICE guideline on antimicrobial stewardship consider reviewing intravenous antibiotic prescriptions at 48 to 72 hours, documenting response to treatment and any available microbiology results to determine if the antibiotic should be continued or switched to a narrower spectrum or an oral antibiotic.

1.2.1 Self-care

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that people should be given verbal advice and written information that they can take away about how to manage their infection themselves at home with self-care if it is safe to do so.

1.2.2 Antibiotic prescribing strategies

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use recommends that when antimicrobials are prescribed, prescribers should:

- Consider supplying antimicrobials in pack sizes that correspond to local (where available) and national guidelines on course lengths.
- Follow local (where available) or national guidelines on prescribing the shortest effective course, the most appropriate dose, and route of administration.
- Undertake a clinical assessment and document the clinical diagnosis (including symptoms) in the patient's record and clinical management plan.
- Document in the patient's records (electronically wherever possible):
  - the reason for prescribing an antimicrobial
  - the plan of care as discussed with the patient, their family member or carer (as appropriate), including the planned duration of any treatment.
- Take into account the benefits and harms for an individual patient associated with the particular antimicrobial, including:
  - possible interactions with other medicines or any food and drink
  - the patient's other illnesses, for example, the need for dose adjustment in a patient with renal impairment
  - any drug allergies (these should be documented in the patient's record)
  - the risk of selection for organisms causing healthcare associated infections, for example, *C. difficile*.
- Document in the patient's records the reasons for the any decision to prescribe outside local (where available) or national guidelines.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population recommends that resources and advice should be available for people who are prescribed antimicrobials to ensure they are taken as instructed at the correct dose, via the correct route, for the time specified. Verbal advice and written information that people can take away about how to use antimicrobials correctly should be given, including:

- not sharing prescription-only antimicrobials with anyone other than the person they were prescribed or supplied for
- not keeping them for use another time
- returning unused antimicrobials to the pharmacy for safe disposal and not flushing them down toilets or sinks.

1.3 Safety netting advice

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population recommends that people with self-limiting infections should be given explicit advice on when to seek medical help, which symptoms should be considered 'red flags' and safety-netting advice. Safety-netting advice should include:

- how long symptoms are likely to last with and without antimicrobials
- what to do if symptoms get worse
- what to do if they experience adverse effects from the treatment
- when they should ask again for medical advice.

1.4 Symptoms and signs of a more serious illness or condition (red flags)

The NICE clinical knowledge summary on pyelonephritis states that people with acute pyelonephritis can be treated in primary care if they are:

- pyrexial but have no risk factors for developing a complication from acute pyelonephritis
- apyrexial, with or without risk factors for developing a complication.

The Clinical Knowledge Summary suggests to admit to hospital people who:

- are significantly dehydrated or who are unable to take oral fluids and medications
- have signs of sepsis
- are pregnant and pyrexial
- are frail, elderly residents in care homes who have recently been hospitalised or who have had recurrent UTI
- fail to improve significantly within 24 hours of starting antibiotics.

Complications of acute pyelonephritis include impaired renal function or renal failure, septicaemia and preterm labour in pregnancy. The NICE clinical knowledge summary on pyelonephritis suggests that the following factors increase the risk of developing a complication:

- severe illness
- age over 65 years
- abnormalities of renal tract anatomy and function
- foreign body within the renal tract, including renal stones and urinary, ureteric, or nephrostomy catheters
- immunocompromised
- diabetes mellitus
- pregnancy
- persistent pyelonephritis despite treatment
- renal impairment.

Information from NHS choices on kidney infection suggests that in rare cases a kidney infection can cause sepsis and a build-up of pus in the kidney (abscess).

2 Evidence selection

A range of evidence sources are used to develop antimicrobial prescribing guidelines. These fall into 2 broad categories:

- Evidence identified from the literature search (see section 2.1 below)
- Evidence identified from other information sources. Examples of other information sources used are shown in the interim process guide (2017).

See appendix A: evidence sources for full details of evidence sources used for pyelonephritis.

2.1 Literature search

An overall literature search for all urinary tract infection (UTI) topics identified 6,695 references (see appendix C: literature search strategy for full details). These references were screened using their titles and abstracts and 59 full text papers were obtained and assessed for relevance. Twenty six full text references of systematic reviews and randomised controlled trials (RCTs) were assessed as relevant to the guideline review question (see appendix B: review protocol). Ten percent of studies were screened to establish inter-rater reliability, and this was within the required threshold of 90%.

The methods for identifying, selecting and prioritising the best available evidence are described in the interim process guide. Fourteen references were prioritised by the Committee as the best available evidence and were included in this evidence review (see appendix F: included studies).

The 12 references that were not prioritised for inclusion are listed in appendix I: not prioritised studies. Also see appendix E: evidence prioritisation for more information on study selection.

The remaining 33 references were excluded. These are listed in appendix J: excluded studies with reasons for their exclusion.

See also appendix D: study flow diagram.

2.2 Summary of included studies

A summary of the included studies is shown in tables 1. Details of the study citation can be found in appendix F: included studies. An overview of the quality assessment of each included study is shown in appendix G: quality assessment of included studies.

Table 1: Summary of included studies: antimicrobials

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Antimicrobials (adults)					
ASPECT-cUTI[a] DB. NI. RCT. 209 sites worldwide. Follow-up at test-of-cure visit (5 to 9 days after end of treatment)	n=800 195 were males	Hospitalised adults (aged ≥18 years) with either APN or complicated UTI	Ceftolozane-tazobactam 1.5 g (IV) every 8 hours for 7 days	Levofloxacin 750 mg (IV) once daily for 7 days	Clinical and microbiological outcomes
Eliakim-Raz et al. 2013 Systematic review and meta-analysis. Multiple countries. Follow-up at multiple time points	n=2,515 8 RCTs Males accounted for between 0% and 39% in included studies	Hospitalised and non-hospitalised adults (aged >16 years) with APN or UTI with sepsis	≤7 days of antibiotic treatment	>7 days of antibiotic treatment	Clinical failure[b] at the end of the long treatment arm
Kyriakidou KG et al. 2008 Systematic review and meta-analysis. Multiple countries. Follow-up at multiple time points	n=283 4 RCTs Males accounted for between 0% and 34% in included studies	Adults and young people (aged ≥ 15 years) with APN (setting not described)	7 to 14 days of antibiotic treatment	14 to 42 days of antibiotic treatment	Clinical and microbiological outcomes
Moramezi F et al. 2008 RCT. Iran. Follow-up time point not described	n=60	Hospitalised pregnant women with APN (ages not described)	Cephalothin 1 g (IV) every 6 hours[c]	Ampicillin 1 g (IV) every 6 hours and gentamicin 80 mg (IV) every 8 hours[c]	Clinical symptoms and signs of APN
Park et al. 2012 DB. RCT. Korea. Follow-up at 5 to 9 days after treatment	n=271 26 were males	Hospitalised adults (aged ≥ 18 years) with APN or complicated UTI	Ertapenem 1 g (IV) once daily[d]	Ceftriaxone 2 g (IV) once daily[d]	Efficacy, tolerability and safety
Pasiechnikov S et al. 2015. RCT. Ukraine. Follow-up time point not described	n=241 Male to female ratio in the PNS group was 1:1.6 and in the US group was 1:2.4	Hospitalised adults (age not adequately reported) with acute obstructive pyelonephritis	Ceftazidime 500 mg (IV) twice daily for 7 to 14 days[e]	Ciprofloxacin 400 mg (IV) twice daily for 7 to 14 days[e]	Clinical and microbiological outcomes

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Peterson J et al. 2008 DB. RCT. USA. Follow-up at end of therapy	n=1,093 427 males	Hospitalised and non-hospitalised adults (aged 18 years or older) with APN or complicated UTI	Levofloxacin 750 mg (IV) or orally once daily for 5 days	Ciprofloxacin 400 mg (IV) and/or ciprofloxacin 500 mg orally twice daily for 10 days	Clinical and microbiological outcomes
Pohl A. 2007 Systematic review and meta-analysis. Multiple countries. Follow-up at multiple time points.	n=1,743 15 RCTs (number of males not reported)	Hospitalised and non-hospitalised adults and children[f] with APN or other severe UTI	Route of administration of antibiotic	Other route of administration of antibiotic	Clinical and microbiological outcomes
Ren H et al. 2017 OL. NI. RCT. Follow-up at end of therapy.	n=317 40 were males	Hospitalised and non-hospitalised adults (aged at least 18 years) with APN or complicated UTI	Levofloxacin 750 mg (IV) for 5 days	Levofloxacin 500 mg (IV then oral) for 7 to 14 days	Clinical outcomes
Talan DA et al. 2000 DB. RCT. USA. Follow-up at 4 to 11 days after treatment.	n=378 No males	Non-hospitalised women (aged at least 18 years) with APN	Ciprofloxacin 500 mg (oral) twice daily for 7 days, with or without an initial IV dose	Trimethoprim/ sulfamethoxazole 160/800 mg (oral) twice daily for 14 days with or without initial IV dose of ceftriaxone 1 g	Clinical and microbiological outcomes
Vazquez JA et al. 2012 DB. RCT. Multiple countries. Follow-up at 5 to 9 days.	n=135 35 were males	Hospitalised adults (aged 18 to 90 years) with acute pyelonephritis or complicated UTI	Ceftazidime-avibactam 500/125 mg (IV) every 8 hours for 7 to 14 days[g]	Imipenem-cilastatin 500 mg (IV) every 6 hours for 7 to 14 days[g]	Microbiological outcome at the test-of-cure visit
Antimicrobials (children)					
Strohmeier Y et al. 2014 Systematic review and meta-analysis. Multiple countries. Follow-up at multiple time points	n=4,452 27 RCTs and quasi-randomised controlled trial (number of males not reported)	Hospitalised and non-hospitalised children (aged 0 to 18 years) with proven APN and UTI, clinical and/or microbiological diagnosis	Different antibiotics, dosing regimens, duration of treatment and routes of administration	Any other antibiotic, dosing regimen, duration of treatment or route of administration	Clinical and microbiological outcomes for oral versus IV followed by oral antibiotics

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Abbreviations: RCT, Randomised controlled trial; DB, Double blind; NI, Non-inferiority; OL, Open label; UTI, Urinary tract infection; APN, Acute pyelonephritis; ASPECT-cUTI, Assessment of the Safety Profile and Efficacy of Ceftolozane-tazobactam in Complicated Urinary Tract Infections study; IV, Intravenous; PNS, Percutaneous nephrostomy; US, Ureteral stent					
[a] Main study papers by Wagenlehner FM et al. 2015. Armstrong ES et al. 2016 and Huntington JA et al. 2016 [b] Lack of resolution of signs and symptoms of UTI or modification of antibiotics at follow-up [c] IV treatment until cessation of fever then switched to cephalexin 500 mg every 6 hours orally [d] After 3 doses of IV (and if patient was improving) then switched to either oral ciprofloxacin 500 mg twice daily or if unable to tolerate or resistant cefixime 200 mg twice daily [e] Initial randomisation was to either PNS or US intervention then subsequent randomisation to antibiotic group [f] See also Antimicrobials (children) [g] At day 4 patients were assessed for switch to oral ciprofloxacin 500mg twice daily or an alternative if intolerant of this or ciprofloxacin resistance was an issue					

3 Clinical effectiveness

Full details of clinical effectiveness are shown in appendix H: GRADE profiles. The main results are summarised below.

3.1 Non-pharmacological interventions

No systematic reviews or randomised controlled trials (RCTs) were identified that assessed non-pharmacological interventions.

3.2 Non-antimicrobial pharmacological interventions

No systematic reviews or RCTs were identified that assessed non-antimicrobial pharmacological interventions.

3.3 Antimicrobials in adults

The evidence review for antimicrobials in adults is based on 4 systematic reviews and 8 (RCTs). The included studies cover antibiotics versus other antibiotics, routes of antibiotic administration and the duration of antibiotic treatment. Five of the studies included only hospitalised adults, 1 study included only non-hospitalised adults, 4 studies included both hospitalised and non-hospitalised adults and 2 studies did not report the setting.

One of the included systematic reviews (Pohl 2007) included both adults and children therefore where analyses include data from studies including children this is stated. There is also some overlap between adults and young people in 2 systematic reviews (Eliakim-Raz et al. 2013 and Kyriakidou et al. 2008) which included people from 15 and 16 years, respectively. Two RCTs (Moramezi et al. 2008 and Pasiechnikov et al. 2015) had inadequate reporting of participants' ages. The proportion of men included in the studies varied from 0% to 39%, with 2 RCTs (Moramezi et al. 2008 and Talan et al. 2000) not including men and 1 systematic review not reporting the proportions of women and men (Pohl 2007).

3.3.1 Back-up antibiotics

No systematic reviews or RCTs were identified in adults that assessed back-up antibiotic prescribing in adults.

3.3.2 Antibiotics compared with placebo

No systematic reviews or RCTs were identified that compared antibiotics with placebo in adults.

3.3.3 Choice of antibiotic

Cephalosporins compared with quinolones

Two RCTs assessed the effectiveness of a cephalosporin compared with a quinolone (Wagenlehner et al. 2015 and Pasiechnikov et al. 2015).

Ceftolozane-tazabactam compared with levofloxacin

One RCT (Wagenlehner et al. 2015) included hospitalised adults (over 18 years) who had pyuria (white blood cells in the urine) and a diagnosis of either acute pyelonephritis or complicated lower urinary tract infection (UTI; defined as all the signs and symptoms of acute pyelonephritis plus suprapubic pain, dysuria, frequency and at least one complicating factor, for example male gender with urinary retention, indwelling urinary catheter, obstructive uropathy or any functional or anatomical urogenital-tract abnormality). The study was limited to mostly women (around 75% of the sample) and less than 20% of participants had a diagnosis of complicated UTI. The intervention was intravenous (IV) antibiotics (either ceftolozane-tazabactam 1.5 g every 8 hours or levofloxacin 750 mg once daily, both for 7 days) and the authors state that there may have been selection bias leading to the inclusion of more serious illness cases than if other routes of administration were considered.

The study found a significantly higher rate of composite cure (clinical cure and microbiological eradication) in all people with either acute pyelonephritis or complicated UTI with ceftolozane-tazabactam at 5 to 9 days after treatment compared with levofloxacin (n=800: 76.9% versus 68.4%, 8.5% difference, 95% confidence interval [CI] 2.3% to 14.6%, number needed to treat [NNT] 12 (95% CI 7 to 43); moderate quality evidence). Microbiological eradication in this population at 5 to 9 days was also significantly higher with ceftolozane-tazabactam compared with levofloxacin (n=800: 80.4% versus 72.1%; 8.3% difference, 95% CI 2.4% to 14.1%, NNT 13 [95% CI 8 to 42]; moderate quality evidence), but there was no significant difference in clinical cure at 5 to 9 days (n=800: 92% versus 88.6%; 3.4% difference, 95% CI −0.7 to 7.6; moderate quality evidence). Sub-group analysis of composite cure at 5 to 9 days for those with complicated UTI was significantly higher with ceftolozane-tazabactam compared with levofloxacin (n=144: 67.1% versus 47.3%; 19.8% difference, 95% CI 3.7% to 34.6%; NNT of 5 [95% CI 3 to 25]; low quality evidence), but there was no significant difference for people with acute pyelonephritis (n=656: 79% versus 73.2%; 5.8% difference, 95% CI −0.7% to 12.3%; moderate quality evidence). Wagenlehner et al. 2015 also found that older adults (aged 65 years and over) with acute pyelonephritis or complicated UTI had significant benefit from ceftolozane-tazabactam compared with levofloxacin (composite cure, n=199: 70% versus 53.5%; 16.5% difference, 95% CI 3% to 29.2%; NNT [95% CI 4 to 32]; low quality evidence), but this significant benefit was not seen in adults younger than 65 years (moderate quality evidence).

Wagenlehner et al. 2015 also found no significant difference in composite cure between groups, in a subgroup of adults with bacteraemia (n=62: 79.3% versus 57.6%, 21.7% difference, 95% CI -1.6% to 41.7%; low quality evidence).

Ceftazidime compared with ciprofloxacin

One RCT (Pasiechnikov et al. 2015) of 241 hospitalised adults with acute obstructive unilateral pyelonephritis (diagnosed with IV urogram and pyeloectasy and the presence of fever, flank tenderness, dysuria and white cells in the urine [pyuria] from kidney drainage) compared ceftazidime 500 mg IV every 12 hours with ciprofloxacin 400 mg IV every 12 hours, both for 7 to 14 days unless a more suitable antibiotic was indicated (based on susceptibility results). The authors also analysed results by the type of surgical kidney drainage patients were randomised to (percutaneous nephrostomy and ureteral stenting).

The RCT found that in people with percutaneous nephrostomy for obstruction in acute pyelonephritis, ceftazidime had a significantly higher rate of clinical cure compared with ciprofloxacin at 5 to 7 days after treatment (n=124: 88.9% versus

73.8%; relative risk [RR] 1.20, 95% CI 1.01 to 1.43, NNT 7 [95% CI 4 to 62]; very low quality evidence) and microbiological cure (n=111: 85.7% versus 67.3%; RR 1.27, 95% CI 1.03 to 1.58, NNT [95% CI 3 to 34]; very low quality evidence). There was also a significantly higher rate of microbiological cure with ceftazidime compared with ciprofloxacin (n=100: 78.4% versus 57.1%; RR 1.37, 95% CI 1.04 to 1.82, p=0.03; NNT of 5 [95% CI 3 to 30]; very low quality evidence). However, in people with ureteral stenting for obstruction in acute pyelonephritis, there was no significant difference between the 2 antibiotic groups (very low quality evidence). The significant differences in clinical and microbiological cure rates were maintained at 20 to 21 days for the percutaneous nephrostomy group but not for the ureteral stenting group[1].

Carbapenems compared with cephalosporins

Two RCTs assessed the effectiveness of a carbapenem compared with a cephalosporin (Park et al. 2012 and Vazquez et al. 2012).

Ertapenem compared with ceftriaxone

An RCT (Park et al. 2012) compared ertapenem 1 g IV once daily with ceftriaxone 2 g IV once daily in hospitalised adults (over 18 years) with acute pyelonephritis or another complicated UTI (signs or symptoms of UTI, pyuria and positive urine culture [>10^5 cfu/mL] in men, additionally indwelling catheter, instrumentation of the urinary tract or functional or anatomical abnormality of the urinary tract in women), both interventions were followed by a switch to an oral antibiotic at day 3, if indicated. The RCT is limited in that it did not assess longer term outcomes (relapse or recurrence); additionally the use of creatinine clearance <30mL/min as an exclusion criteria may have excluded older adults with declining renal function due to their age. The study included mainly women (74%) and 63% of participants had acute pyelonephritis.

Park et al. (2012) found no significant difference in microbiological response at 5 to 9 days with ertapenem compared with ceftriaxone (n=137: 88.7% versus 87.9%; 0.8% difference, 95% CI −11.7 to 10.2; high quality evidence). No differences in microbiological response rates between ertapenem and ceftriaxone were found in sub-group analyses of people with acute pyelonephritis at 5 to 9 days (high quality evidence) or those with complicated UTI (moderate quality evidence). There were also no significant differences in clinical cure and favourable microbiological response at early follow-up (moderate quality evidence) or discontinuation of IV treatment (high quality evidence).

Park et al. (2012) also found no difference in favourable microbiological response between groups in a subgroup of adults with bacteraemia at 5 to 9 days after treatment (n=44: 81% versus 82.6%; 1.6% difference, 95% CI not reported; low quality evidence).

Ceftazidime-avibactam compared with imipenem-cilastatin

One RCT (Vazquez et al. 2012) compared ceftazidime-avibactam (500/125 mg IV every 8 hours) with imipenem-cilastatin (500 mg IV every 6 hours) for complicated UTI, including pyelonephritis, in hospitalised adults (aged 18 to 90 years). Complicated UTI was defined as symptoms and signs of UTI, pyuria (≥10 white blood cells/mm^3) and a positive urine culture (≥10^5 cfu/mL), with women requiring a history of urological abnormalities (catheterisation) and/or functional or anatomical

[1] The author's paper uses odds ratios (OR) which could not be replicated by NICE analysis. The authors recognise that the ORs in the paper may contain overestimation but assert this does not change the principal outcomes of the study, personal communication 25/05/2017. Risk ratios are NICE analysis.

abnormalities of the urinary tract. The study is limited by its small sample size, which is smaller than the size calculated by the authors as needed to estimate efficacy and safety in the study.

Vazquez et al. 2012 found no significant difference in favourable microbiological response in the microbiologically evaluable population at 5 to 9 days (n=62: 70.4% versus 71.4%; 1.1% difference, 95% CI −27.2% to 25%; low quality evidence). There were no significant differences in favourable microbiological response between ceftazidime-avibactam and imipenem-cilastatin in sub-group analyses of those with acute pyelonephritis (low quality evidence) or complicated UTI (very low quality evidence). There was also no difference in clinical response at either the test-of-cure visit or at late follow-up (low quality evidence).

Cephalosporin compared with a broad spectrum penicillin plus aminoglycoside

One RCT (Moramezi et al. 2008) compared cephalothin (1 g IV every 6 hours) with ampicillin (1 g IV every 6 hours) plus gentamicin (80 mg IV every 8 hours) for treating pregnant women with pyelonephritis which was clinically and microbiologically diagnosed (pyuria and culture, definitions not described). Most of the women in the study were in the second (57%) or third (28%) trimester, and most were primiparous (83%). The study is limited by a small sample size (no sample size calculation is described), poor description of the study methods (randomisation, blinding, allocation concealment and statistical analysis methods) and reporting of outcomes.

There were no significant differences between groups in either the duration of clinical lower urinary tract symptoms (n=60: mean difference 1.2 hours, p=not significant; very low quality evidence) or the mean duration of costovertebral angle tenderness (n=60: mean difference of 8 hours, p=not significant; very low quality evidence). However, the mean duration of time to end of fever was significantly better with ampicillin-gentamicin compared with cephalothin (n=60: mean 11 hours lower, p=0.01; very low quality evidence).

Quinolone compared with another quinolone

One RCT (Peterson et al. 2008) compared levofloxacin (750 mg IV or orally once daily for 5 days) with ciprofloxacin (400 mg IV or 500 mg orally twice daily for 10 days) in hospitalised and non-hospitalised adults (18 years and over) with acute pyelonephritis and/or complicated UTI (for women, defined as at least 1 of neurogenic bladder, urinary retention, partial obstruction, renal tumour or fibrosis, distorted urethral structure and/or intermittent catheterisation). Diagnosis was clinical and microbiological (≥10^5 cfu/mL of 1 or 2 uropathogens). The study sample had more women (61%) than men and most participants had complicated UTI (71.5%). The study was limited by the longer course of treatment in the ciprofloxacin group.

At ‘post treatment’ (study days 15 to 19) there was no significant difference between groups for microbiological eradication (n=619: 79.8% versus 79.8%; 0% difference, 95% CI −6.3% to 6.3%; high quality evidence) or clinical success (n=619: 81.1% versus 80.1%; 0.9% difference, 95% CI −7.2% to 5.3%; high quality evidence). There was also no significant difference between groups at end of therapy (study days 5 to 7) in microbiological eradication (high quality evidence) or clinical success (high quality evidence).

Quinolone compared with co-trimoxazole

One RCT (Talan et al. 2000) compared oral ciprofloxacin (500 mg twice daily for 7 days) with oral co-trimoxazole (160/800 mg twice daily for 14 days) with or without initial IV doses for acute pyelonephritis in hospitalised or non-hospitalised premenopausal women only (over 18 years). Diagnosis was made clinically, although urine samples were taken for culture (>10^3 cfu/mL) and those without a causative organism were discontinued from the study.

At 4 to 11 days after treatment there was a significant difference favouring ciprofloxacin in continued bacteriologic cure (n=214: 99.1% versus 89.1%; 10% difference, p=0.004, 95% CI 0.04 to 0.16; NNT 10 [95% CI 7 to 28]; moderate quality evidence) and continued clinical cure (n=224: 96.5% versus 82.9%; 13% difference, p=0.002, 95% CI 0.06 to 0.22; NNT 8 [95% CI 5 to 18]; low quality evidence). These differences remained statistically significant at 22 to 48 days for clinical cure, but not for bacteriological cure (low quality evidence).

3.3.4 Antibiotic dosing and course length

Two systematic reviews (Eliakim-Raz et al. 2013 and Kyriakidou et al. 2008) and 1 RCT (Ren et al. 2017) assessed the evidence on antibiotic dosing and course length in adults.

One systematic review (Eliakim-Raz et al. 2013) of 8 RCTs compared short-course antibiotics for 7 days or less with long-course antibiotics (10 days to 6 weeks) in people 16 years and over with acute pyelonephritis and septic UTI. The included RCTs compared a range of different antibiotics:

- ciprofloxacin 500 mg twice daily for 7 days versus 14 days
- levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400/500 mg twice daily for 10 days
- levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400 mg twice daily for 10 days
- ciprofloxacin 500 mg twice daily for 7 days versus co-trimoxazole 160/800 mg twice daily for 14 days
- ceftriaxone plus cefixime 1 g IV/400 mg orally once daily for 7 days versus 14 days
- fleroxacin 400 mg once daily for 7 days versus 14 days
- pivampicillin 0.25 g plus pivmecillinam 0.2 g 2 tablets three times daily for 7 days versus pivampicillin 0.25 g plus pivmecillinam 0.2 g 2 tablets daily for 7 days then 1 tablet for days 8 to 21, 3 times daily
- ampicillin 10 g three times daily for 3 days then twice daily for 4 days versus continued ampicillin or pivampicillin for up to 6 weeks

The studies were in hospitalised and non-hospitalised adults but were limited to mainly women (0% to 39% were men).

The review found no significant difference between short and long-course antibiotics in clinical failure, either at end of completion of the long course (5 RCTs, n=1,076: RR 0.63, 95% CI 0.33 to 1.18; low quality evidence) or at the end of follow-up (7 RCTs, n=1,398: RR 0.79, 95% CI 0.56 to 1.12; low quality evidence).

One study of ciprofloxacin for 7 days versus co-trimoxazole for 14 days accounting for 21.5% and 35.8% of the weight in the 2 meta-analyses favoured short-course antibiotic in both analyses (RR 0.21, 95% CI 0.07 to 0.59; RR 0.42, 95% CI 0.21 to 0.83). There was also no significant difference in microbiological failure at the end of follow-up (8 RCTs, n=1,402: RR 1.16, 95% CI 0.83 to 1.62; low quality evidence).

One study of pivampicillin plus pivmecillinam for 7 days versus pivampicillin and pivmecillinam for up to 21 days accounting for 13.5% of the weight in the meta-analysis favoured long-course antibiotic (RR 2.61, 95% CI 1.39 to 4.88, NNT 3 [95% CI 2 to 5]). There were lower rates of microbiological failure with long-course antibiotics (10 days to 6 weeks) compared with short courses of 7 days or less in the treatment of acute pyelonephritis and septic UTI in those aged 16 years and older with urogenital abnormality (1 RCT, n≈100: RR 1.78, 95% CI 1.02 to 3.10; very low quality evidence). The systematic review also found no difference in clinical failure with antibiotic treatment for 7 days or less compared with longer courses in the treatment of acute pyelonephritis and septic UTI in those aged 16 years and older with bacteraemia (sub-group analysis; 4 RCTs, n=86: RR 0.54, 95% CI 0.15 to 1.92; very low quality evidence).

Kyriakidou et al. (2008) included 4 RCTs of the same antibiotic regimen but with different course lengths (7 to 14 days compared with 14 to 42 days) in young people and adults (aged ≥15 years) with acute pyelonephritis. The included RCTs compared a range of antibiotics used in different regimens (fleroxacin 400 mg once daily for 7 days versus 14 days; ampicillin 500 mg four times daily or co-trimoxazole 160/800 mg twice daily for 14 days versus 6 weeks; pivampicillin and pivmecillinam for 7 days versus pivampicillin and pivmecillinam for up to 21 days; gentamicin or tobramycin 1.5 to 1.75 mg/kg three times daily for 48 to 72 hours followed by oral co-trimoxazole or ampicillin or cephalexin for 7 to 8 days versus 18 to 19 days). Studies were limited to mostly females in (0% to 33% male in studies) and the setting was hospital and non-hospital. The review found no significant difference in clinical success at test-of-cure visit (4 RCTs, n=199: odds ratio [OR] 1.27, 95% CI 0.59 to 2.7; moderate quality evidence) or in bacteriologic efficacy (4 RCTs, n=199: OR 0.80, 95% CI 0.13 to 4.95; very low quality evidence). One study of pivampicillin and pivmecillinam for 7 days versus pivampicillin and pivmecillinam for up to 21 days accounting for 35.97% of the weight in the meta-analysis favoured longer treatment for bacteriologic efficacy (OR 0.18, 95% CI 0.06 to 0.53; moderate quality evidence). There were also no significant differences between groups in the rate of relapse between test-of-cure and follow-up visits or the rates or recurrence (very low quality evidence).

One RCT (Ren et al. 2017) of treatment of complicated UTI and acute pyelonephritis (diagnostic criteria not defined) in hospitalised and non-hospitalised adults (aged at least 18 years) compared a short course (5 days) of intravenous levofloxacin (750 mg once daily) with 7 to 14 days of intravenous/oral levofloxacin (500 mg once daily). The study was limited to mostly females (>80%) and is at risk of inclusion bias as investigators could exclude patients without clear reason. There was no significant difference between groups in clinical effectiveness at the end of treatment (n=317: 89.87% versus 89.31%, 0.57% difference, 95% CI −6.16% to 7.29%, moderate quality evidence). Microbiological eradication was not significantly different between groups (n=140: 89.6% versus 86.3%, p>0.05; moderate quality evidence) and there was no significant difference in the time to clinical success (n=317: 1 day median difference, p>0.05; moderate quality evidence). The clinical success rates were significantly higher for acute pyelonephritis than for complicated UTI in both dose groups (p<0.05 for both comparisons; very low quality evidence) but not significantly different for the different dose regimens for either acute pyelonephritis or complicated UTI group.

3.3.5 Route of antibiotic administration

The evidence review for route of antibiotic administration in adults with acute pyelonephritis and complicated UTI (severe symptomatic UTI) is based on 1 systematic review of 15 RCTs (Pohl 2007). This review also included RCTs involving children in the analyses. Included studies assessed the following routes of administration:

- oral antibiotics
- single doses of injectable antibiotics (IV or intramuscular [IM] antibiotics) followed by oral antibiotics
- sequential IV antibiotics followed by oral antibiotics
- injectable antibiotics.

The review identified outcomes at 3 time points (under therapy, at end of therapy and after an interval) but the definition of these time points is not discussed or defined in the review.

Sequential intravenous then oral antibiotics compared with intravenous or intramuscular antibiotics

Evidence from 3 RCTs in a systematic review (Pohl 2007) compared sequential intravenous then oral antibiotics with IV or IM antibiotics in people with severe symptomatic UTI:

- ciprofloxacin IV for 2 to 5 days then oral ciprofloxacin for up to 14 days compared with ceftazidime IV for 4 to 9 days;
- ceftriaxone IV for 4 days then oral cefixime for 11 days compared with ceftriaxone IV for 4 days then ceftriaxone IV or IM for 11 days;
- ceftriaxone IV until afebrile for >24 to 48 hours then oral ceftibuten for 10 days compared with ceftriaxone IV for 10 days.

There were no significant differences in clinical cure at 'end of therapy' (2 RCTs [adults], n=137: RR 1.01, 95% CI 0.94 to 1.10; moderate quality evidence) or bacteriological cure at 'end of therapy' (2 RCTs [1 in adults and 1 in children], n=76: RR 1.05, 95% CI 0.95 to 1.17; moderate quality evidence) between sequential intravenous then oral antibiotics and IV or IM antibiotics. There was also no significant difference between groups in re-infection at 'end of therapy' (1 RCT [adults], n=72: RR 1.00, 95% CI 0.15 to 6.72) or in relapse after an interval (3 RCTs [1 in adults and 2 in children], n=203: RR 2.79, 95% CI 0.3 to 25.67; very low quality evidence).

Sequential intravenous then oral antibiotics compared with oral antibiotics

Evidence from 3 RCTs in Pohl 2007 compared sequential intravenous then oral antibiotics with oral antibiotics in people with severe symptomatic UTI:

- cefotaxime IV for 3 days (or until afebrile >24 hours) then oral cefixime for 14 days compared with oral cefixime for 14 days;
- ciprofloxacin IV for 72 hours (or until afebrile >24 hours) then oral ciprofloxacin compared with oral ciprofloxacin;
- ceftriaxone IV for 3 days then oral ceftibuten for 11 days compared with oral ceftibuten for 14 days.

There were no significant differences between groups in clinical or bacteriological cure 'under therapy' (3 RCTs [2 in children and 1 in adults], n=599: RR 1.00, 95% CI 0.98 to 1.02; moderate quality evidence).

Oral antibiotics compared with intravenous or intramuscular antibiotics

Evidence from 1 RCT in Pohl (2007) compared oral antibiotics (norfloxacin for 7 days) with IV or IM antibiotics (aztreonam IM for 7 days) in people with severe symptomatic UTI. It found that IV or IM antibiotics were significantly better for bacteriological cure than oral antibiotics at ‘end of therapy’ (1 RCT, n=38: RR 1.37, 95% CI 1.02 to 1.84, NNT 4 (95% CI 3 to 15); low quality evidence), and that ‘after an interval’ this effect appeared to be greater, although the 95% CI for both results overlap (RR 1.95, 95% CI 1.24 to 3.08, NNT [95% CI 2 to 4]; very low quality evidence).

Single dose intravenous or intramuscular then oral antibiotics compared with sequential intravenous then oral antibiotics

Evidence from 2 RCTs in Pohl 2007 compared single-dose IV or IM antibiotics then oral antibiotics with sequential intravenous then oral antibiotics in people with severe symptomatic UTI:

- single-dose ceftriaxone IM used twice within 18 to 36 hours then oral cefalexin for 10 days compared with cefazolin IV (until afebrile for >48 hours) then cefalexin for 10 days;
- single-dose ceftriaxone IV then oral cefixime 400 mg or other antibiotic according to sensitivities for 10 days compared with ceftriaxone IV until results of urine culture available, then oral antibiotics for 10 days.

There were no significant differences in clinical cure ‘under therapy’ (2 RCTs [adults], n=225: RR 0.93, 95% CI 0.86 to 1.02; moderate quality evidence) or bacterial eradication at ‘end of therapy’ (1 RCT [adults], n=110: RR 0.96, 95% CI 0.79 to 1.16; moderate quality evidence) between groups. There was also no significant difference in the mean time to cessation of fever (1 RCT [adults], n=105: mean difference 0.10 days, 95% CI 0.19 to 0.39; low quality evidence) or duration of symptoms (1 RCT [adults], n=105: 95% CI 0.30 days, 95% CI 0.16 to 0.76; low quality evidence).

3.4 Antimicrobials in children

The evidence review for antimicrobials in children with acute pyelonephritis is based on 1 systematic review of 27 RCTs (Strohmeier et al. 2014). It is noted that the systematic review by Pohl (2007) also contained outcomes for children but this study was not prioritised as more recent evidence in children was available from the review by Strohmeier et al (2014). No evidence was found for complicated UTI in children. Most of the studies were limited by excluding children with impaired kidney function (12 RCTs) and children with known severe urinary tract abnormality (14 RCT).

3.4.1 Back-up antibiotics

No systematic reviews or RCTs were identified in adults that assessed back-up antibiotic prescribing in children.

3.4.2 Antibiotics compared with placebo

No systematic reviews or RCTs were identified that compared antibiotics with placebo in children.

3.4.3 Choice of antibiotic

A systematic review (Strohmeier et al. 2014) found no significant difference in the number of children with persistent bacteriuria after 48 hours of treatment with a third generation cephalosporin (intravenous [IV] cefotaxime 25 mg/kg four times daily for 14 days, oral cefetamet pivoxil 10 or 20 mg/kg twice daily for 7 to 10 days or oral ceftibuten 9 mg/kg once daily for 10 days) compared with co-amoxiclav (25 mg/kg IV four times daily for 7 days then 50 mg/kg/day orally for 7 days; 30 to 50 mg/kg three times daily for 7 to 10 days) or co-trimoxazole (3 to 15 mg/kg twice daily for 10 days) (3 RCTs, n=439: RR 2.41, 95% CI 0.98 to 5.93; low quality evidence). There were no significant differences between groups for either recurrence of UTI at 4 to 10 days after treatment (4 RCTs, n=491: RR 1.23, 95% CI 0.32 to 4.74; very low quality evidence) or persistent fever for more than 48 hours (1 RCT, n=20: RR 5.00, 95% CI 0.27 to 92.62, very low quality evidence). A significantly greater number of children had persistent symptoms after the end of treatment with other antibiotics compared with third generation cephalosporins (3 RCTs, n=471: RR 0.28, 95% CI 0.13 to 0.62, NNT 14 [95% CI 8 to 42]; moderate quality evidence); however one study accounted for 93.6% of the weight in the meta-analysis (the comparator antibiotic was co-trimoxazole).

There were no significant differences between a fourth generation cephalosporin (IV cefepime 50 mg/kg three times daily and a third generation cephalosporin (IV ceftazidime 50 mg/kg three times daily until afebrile for 48 hours, followed by oral co-trimoxazole for 10 to 14 days until afebrile for persistent or recurrent bacteriuria at any time point, including 5 to 9 days after treatment (1 RCT, n=187: RR 2.37, 95% CI 0.47 to 11.91; very low quality evidence), or in recurrent UTI with a different pathogen (1 RCT, n=235: RR 1.19, 95% CI 0.45 to 3.18; very low quality evidence), or for unsatisfactory clinical response at any time point including 5 to 9 days after treatment (1 RCT, n=199: RR 5.05, 95% CI 0.25 to 103.87; very low quality evidence). However there is considerable uncertainty around these results.

Strohmeier et al. (2014) included a single RCT that compared 2 different third generation cephalosporins (IV ceftriaxone 50 mg/kg daily for 10 days compared with IV cefotaxime 50 mg/kg twice daily for 10 days). No children had persistent bacteriuria at 48 hours in either group (n=100). No significant difference between groups was found for bacteriuria 10 days after the end of treatment (n=83: RR 0.87, 95% CI 0.37 to 2.03; very low quality evidence) or UTI 1 month after treatment (n=81: RR 0.68, 95% CI 0.30 to 1.50; very low quality evidence).

One small RCT included in Strohmeier et al. (2014) compared the aminoglycoside antibiotics isepamicin (IV 7.5 mg/kg twice daily for 10 to 14 days) and amikacin (IV 7.5 mg/kg twice daily for 10 to 14 days), both administered alone or in combination with another antibiotic. No children in the study had persistent bacteriuria after 48 hours, 7 days or 30 days after treatment (n=16, as no child had the outcome analysis was not possible; very low quality evidence). Additionally, no children developed hearing loss on testing (very low quality evidence). The mean time to resolution of fever was the same in both groups (24 hours; very low quality evidence). However, there is considerable uncertainty about these results due to the very small numbers of children.

3.4.4 Frequency of antibiotic dosing

A systematic review (Strohmeier et al. 2014) included 3 RCTs that compared once daily administration of an aminoglycoside (gentamicin IV 5 to 7.5 mg/kg depending on child age, until afebrile or for 2 to 3 days, or IV netilmicin 2 to 6 mg/kg daily dose for 10 days) with 8 hourly administration of an aminoglycoside. There were no significant differences between groups in the risk of persisting bacteriuria 1 to 3 days after com treatment (3 RCTs, n=435: RR 1.05, 95% CI 0.15 to 7.27, very low quality evidence) or at 1 week (1 RCT, n=144: RR 2.84, 95% CI 0.12 to 68.57; very low quality evidence).

Strohmeier et al (2014) also found no significant difference between groups in persisting clinical symptoms after 3 days of treatment, recurrent UTI at 1 month and mean time to resolution of fever in 1 RCT (n=172: mean difference 2.40 hours, 95% CI −7.90 to 12.70: moderate quality evidence). However, the median time to resolution of fever reported in 1 RCT was 27 hours (interquartile range 15 to 48 hours) in the once daily group and 33 hours (interquartile range 12 to 48 hours) in the 8 hourly group (very low quality evidence).

3.4.5 Antibiotic course length

One RCT included in the systematic review by Strohmeier et al (2014) found a significant difference favouring longer courses of antibiotics in recurrence of UTI within 1 month of the end of treatment with sulphafurazole (150 to 200 mg/kg/day in 3 divided doses) for 10 days compared with 42 days (n=149: RR 17.70, 95% CI 2.42 to 129.61, NNT 5 [95% CI 4 to 9]; moderate quality evidence). The number of children with UTI after 1 month until 12 months was not significantly different between groups (n=149: RR 0.87, 95% CI 0.40 to 1.88; very low quality evidence). This antibiotic is not available in the UK.

Strohmeier et al. 2014 found no significant difference in the number of children with persistent bacteriuria after treatment with a single dose of injected antibiotic (gentamicin 3 mg/kg or cefotaxime 50 mg/kg) compared with 7 to 10 days of oral antibiotics (choice was according to sensitivities but included co-trimoxazole, amoxicillin, cephalosporins, nalidixic acid, nitrofurantoin and gentamicin) in 2 RCTs (n=35: RR 1.73, 95% CI 0.18 to 16.30; very low quality evidence). No significant difference was found between groups for recurrence of UTI within 6 weeks (2 RCTs, n=35: RR 0.24, 95% CI 0.03 to 1.97; very low quality evidence).

One RCT included in Strohmeier et al. 2014 found no significant difference in persistent or recurrent bacteriuria with 3 weeks compared with 2 weeks of antibiotics (choice was according to sensitivities and not reported) in children with acute lobar nephronia (n=80, RR 0.07, 95% CI 0.00 to 1.19; very low quality evidence). There was also no significant difference in the recurrence of clinical symptoms with bacteriuria (n=80, RR 0.21, 95% CI 0.01 to 4.24, very low quality evidence).

One further RCT compared 3 days of oral antibiotics (with ampicillin, cephalexin or sulphisoxazole) with 10 days of oral antibiotics. The RCT included a low number of children with acute pyelonephritis and the authors of the systematic review could not include the study in any meta-analyses. Cure was seen in 4 out of 5 children in the 3 days group compared with 5 out of 6 children in the 10 days group (very low quality evidence).

3.4.6 Route of antibiotic administration

A systematic review (Strohmeier et al. 2014) included RCTs that assessed different routes of administration in children with acute pyelonephritis. This included:

- oral antibiotics
- single doses of injected (IV or IM) antibiotics followed by oral antibiotics
- sequential IV antibiotics followed by oral antibiotics
- injected antibiotics

- rectal antibiotics.

Oral antibiotics compared with sequential intravenous then oral antibiotics

Strohmeier et al. (2014) included 4 RCTs that compared oral antibiotics (cefixime for 10 or 14 days, ceftibuten for 14 days or co-amoxiclav for 10 days), with sequential IV antibiotics then oral antibiotics (cefotaxime IV for 3 days or until afebrile then oral cefixime for 13 days; or ceftriaxone IV until resolution of fever or for 3 to 4 days, then oral antibiotics [co-amoxiclav until day 10, ceftibuten for 11 days or cefixime for 6 days]).

There were no significant differences between groups in time to resolution of fever (2 RCTs, n=808: mean difference 2.05 hours, 95% CI −0.84 to 4.94; moderate quality evidence) or fever at day 3 (1 RCT, n=152: RR 0.79, 95% CI 0.30 to 2.06; very low quality evidence). There was also no significant difference in the number of children with persistent UTI at 72 hours after starting treatment (2 RCTs, n=542: RR 1.10, 95% CI 0.07 to 17.41; very low quality evidence). There were no significant differences between groups in the rate of symptomatic UTI within 6 months (very low quality evidence) and the rate of kidney damage at 6 to 12 months (very low quality evidence).

However, in post hoc sub-group analysis in children with vesicoureteral reflux (grades III and IV), oral antibiotics may increase the risk of kidney damage at 6 months compared with intravenous antibiotics (1 RCT, n=46, RR 7.33, 95% CI 1.00 to 54.01, p=0.05; low quality evidence), although there is considerable uncertainty in this result.

Sequential intravenous (3 to 4 days) then oral antibiotics compared with intravenous antibiotics (7 to 14 days)

Strohmeier et al. (2014) included 6 RCTs that compared sequential intravenous antibiotics (for 3 to 4 days) then oral antibiotics, with a longer course of intravenous antibiotics (7 to 14 days). The comparisons were:

- ceftriaxone IV for 3 days then oral cefixime for 12 days compared with ceftriaxone IV for 10 days then oral cefixime for 5 days;
- netilmicin IV for 2 days plus ceftriaxone IV for 3 days, then oral antibiotics according to sensitivities for 5 days compared with IV netilmicin for 2 days and ceftriaxone IV for 8 days;
- ceftriaxone IV daily for 1 to 4 days plus netilmicin IV daily then oral cefixime for days 5 to 10 compared with ceftriaxone IV plus netilmicin IV for 1 to 4 days then ceftriaxone IV for days 5 to 10;
- temocillin IV for 3 days then oral amoxicillin or co-amoxiclav for 18 days compared with temocillin IV for 7 days then oral amoxicillin or co-amoxiclav for 14 days;
- ceftriaxone IV for 2 to 3 days then oral cefixime for 8 days compared with amikacin IV or gentamicin IV, plus ampicillin IV for 10 days;
- ceftriaxone IV until afebrile then oral ceftibuten for a total of 10 days compared with ceftriaxone IV for 10 days).

There was no significant difference between groups in persistent bacteriuria at the end of treatment (4 RCTs, n=305: RR 0.78, 95% CI 0.24 to 2.55, p=0.68, very low quality evidence), recurrent UTI within 6 months (5 RCTs, n=993: RR 0.97, 95% CI 0.58 to 1.62, p=0.92; very low quality evidence) or kidney damage at 3 to 6 months (4 RCTs, n=726: RR 1.01, 95% CI 0.80 to 1.29, p=0.91; low quality evidence). There were also no significant differences in post-hoc sub-group analyses of children with and without vesicoureteral reflux, by age or by delay in treatment.

Single dose intramuscular then oral antibiotics compared with oral antibiotics

One RCT included in Strohmeier et al. (2014) found no significant differences with a single-dose IM antibiotic (ceftriaxone) then an oral antibiotic (co-trimoxazole for 10 days) compared with an oral antibiotic (co-trimoxazole for 10 days) for persistence of bacteriuria after 48 hours (n=69: RR 0.77, 95% CI 0.19 to 3.20; very low quality evidence) or persistence of clinical symptoms (n=69: RR 0.82, 95% CI 0.24 to 2.81; very low quality evidence). The study reported that no children developed symptomatic UTI in the month following treatment in either group.

Oral antibiotics compared with rectal antibiotics

One RCT included in Strohmeier et al. (2014) found no significant differences between oral ampicillin for 5 days and ampicillin suppositories for 5 days for persistence of clinical symptoms (n=105: RR 0.89, 95% CI 0.51 to 1.56; very low quality evidence) or persistence of bacteriuria (n=105: RR 0.89, 95% CI 0.53 to 1.50; very low quality evidence).

4 Safety and tolerability

Details of safety and tolerability outcomes from studies included in the evidence review are shown in appendix H: GRADE profiles. The main results are summarised below.

See the summaries of product characteristics, British National Formulary (BNF) and BNF for children (BNF-C) for information on contraindications, cautions and adverse effects of individual medicines, and for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breastfeeding.

4.1 Non-pharmacological interventions

No systematic reviews or randomised controlled trials (RCTs) were identified in adults that compared non-pharmacological interventions.

4.2 Non-antimicrobial pharmacological interventions

No systematic reviews or RCTs were identified in adults that compared non-antimicrobial pharmacological interventions.

4.3 Antimicrobials

Antibiotic-associated diarrhoea is estimated to occur in 2 to 25% of people taking antibiotics, depending on the antibiotic used (NICE clinical knowledge summary [CKS]: diarrhoea – antibiotic associated).

Allergic reactions to penicillins (such as phenoxymethylpenicillin) occur in 1 to 10% of treated people and anaphylactic reactions occur in less than 0.05% (BNF April 2018). People with a history of atopic allergy (for example, asthma, eczema, and hay fever) are at a higher risk of anaphylactic reactions to penicillins. People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta-lactam antibiotics. See the NICE guideline on drug allergy: diagnosis and management for more information.

Quinolones, including ciprofloxacin, cause arthropathy in the weight-bearing joints of immature animals and are generally not recommended in children or young people who are growing (BNF April 2018).

Nitrofurantoin should be used with caution in those with renal impairment. Adults (especially the elderly) and children on long-term treatment should be monitored for liver function and pulmonary symptoms, with nitrofurantoin discontinued if there is a deterioration in lung function (BNF April 2018).

Trimethoprim has a teratogenic risk in the first trimester of pregnancy (folate antagonist), and manufacturers advise avoidance during pregnancy (BNF April 2018).

Co-trimoxazole is currently under restriction for use in the UK. It is advised that it only be used in urinary tract infections (UTI) where there is bacteriological evidence of sensitivity to co-trimoxazole. Co-trimoxazole should be used with caution in those with asthma, or people with blood disorders, GP6D deficiency or infants under 6 weeks (except for treatment or prophylaxis of pneumocystis pneumonia) (BNF April 2018).

Aminoglycosides are not absorbed from the gut and must be given by injection for systemic infections. Gentamicin is the aminoglycoside of choice in the UK loading and maintenance doses are calculated on the basis of the patient's weight and renal function, with adjustments made according to serum-gentamicin concentrations. Whenever possible treatment should not exceed 7 days. Amikacin is used in the treatment of serious infections caused by gentamicin-resistant Gram-negative bacilli (BNF April 2018).

4.3.1 Antibiotics in adults

Evidence from 2 RCTs (Wagenlehner et al. 2015 and Pasiechnikov et al. 2015) found inconsistent evidence in reported total adverse events. Low quality evidence from 1 RCT (Wagenlehner et al. 2015) found no significant difference in reported total adverse events[2] (30.2% in the ceftolozane-tazabactam group versus 26.5% in the levofloxacin group, relative risk (RR) 1.14, 95% confidence interval (CI) 0.94 to 1.38; low quality evidence). Adverse events were mainly mild to moderate (headache and gastrointestinal symptoms). There were serious adverse effects in 2.8% and 3.4% of the ceftolozane-tazabactam and levofloxacin groups respectively, only 2 of which (*Clostridium difficile* infections) were judged by the authors to be treatment related. Very low quality evidence from another RCT (Pasiechnikov et al. 2015) found that 11.8% of those receiving ciprofloxacin had an adverse effect (mainly central nervous system side effects such as headache, taste disturbance or eye discomfort) while only 4.1% of those receiving ceftazidime (mainly gastrointestinal side effects) had an adverse effect of treatment ($p<0.05$). No serious adverse effects were reported.

Two RCTs (Park et al. 2012 and Vazquez et al. 2012) compared carbapenems with cephalosporins. Park et al. 2012 found no significant difference in total adverse effects in adults taking ertapenem compared with ceftriaxone (n=267, 10.6% versus 4.4%, NICE analysis: RR 2.39, 95% CI 0.95 to 6.02; low quality evidence). Vazquez et al. 2012 found no significant difference in adverse effects in adults taking ceftazidime-avibactam compared with imipenem-cilastatin (n=135, 67.6% versus 76.1%, NICE analysis: RR 0.89, 95% CI 0.72 to 1.10; moderate quality evidence). There were a number of serious adverse events (6/68 in the ceftazidime-avibactam group and 2/67 in the imipenem-cilastatin group); however the difference between groups was not statistically significant (NICE analysis: RR 2.96, 95% CI 0.62 to 14.13, p=0.17; low quality evidence).

Evidence from 1 RCT (Peterson et al. 2008) found no significant difference between levofloxacin and ciprofloxacin for adverse events (35.5% versus 33.1%, 95% CI -7.9% to 3.3%; NICE analysis: RR 1.07, 95% CI 0.91 to 1.27; very low quality evidence). Treatment related adverse events were mainly mild (nausea, headache and gastrointestinal symptoms). Serious adverse events were reported in 17 people treated with levofloxacin and 15 of those treated with ciprofloxacin (NICE analysis: RR 1.17, 95% CI 0.59 to 2.31; low quality evidence). Only 1 serious adverse event (allergy reaction) was considered by the authors to be treatment related. Two deaths occurred during the course of the study (1 in each group) but neither was related to treatment.

One RCT (Talan et al. 2000) in women with acute pyelonephritis found significantly fewer adverse effects with ciprofloxacin compared with co-trimoxazole (24% versus 33%; NICE analysis RR 0.73, 95% CI 0.53 to 1.00; low quality evidence). More people treated with co-trimoxazole than ciprofloxacin had to discontinue study drug

[2] The author's report 185 of 533 (34.7%) in the ceftolozane-tazobactam group and 184 of 535 (34.4%) in the levofloxacin group had adverse events, this does not match the 161 of 533 and 142 of 535 reported in table 3 of the author's study, table data used in NICE analysis.

treatment due to adverse events but this was not significant (11.2% versus 5.7%; NICE analysis: RR 0.51, 95% CI 0.25 to 1.03; low quality evidence).

No evidence from the single RCT comparing cephalothin with ampicillin plus gentamicin was presented for safety and tolerability outcomes (Moramezi et al. 2008).

Antibiotic course length

One systematic review (Eliakim-Raz et al. 2013) found no significant difference in adverse effects between 7 days or fewer and 7 days or longer courses of antibiotics (7 RCTs, n=2,127: RR 0.93, 95% CI 0.73 to 1.18; low quality evidence) or in adverse events requiring discontinuation of antibiotics (7 RCTs, n=2,127: RR 0.78, 95% CI 0.52 to 1.18; low quality evidence). There were no significant differences for either outcome when analyses were limited to quinolones or excluded studies involving co-trimoxazole. Very low quality evidence from another systematic review (Kyriakidou et al. 2008) found no significant difference in adverse events between 7 to 14 days of antibiotics and longer courses (14 to 42 days) of antibiotics (4 RCTs, n=258: RR 0.64, 95% CI 0.33 to 1.25), and there was no significant difference in withdrawal due to adverse events (4 RCTs, n=258: RR 0.65, 95% CI 0.28 to 1.55; very low quality evidence).

The single RCT (Ren et al. 2017) of 5 days of treatment compared with 14 days of treatment with levofloxacin found no significant difference in the proportion of people with adverse events (n=329, 22% versus 23%, RR 0.95, 95% CI 0.64 to 1.42; very low quality evidence) and no significant differences in relation to either severe adverse events (n=329, 1.21% versus 0.61%, p=1.00; very low quality evidence) or the proportion of adverse events related to treatment (n=329, 15.7% versus 18.9%, p=0.071; very low quality evidence).

Route of antibiotic administration

1 systematic review (Pohl 2007) found no significant difference in adverse events between:

- sequential intravenous then oral antibiotics compared with injected antibiotics (4 RCTs, n=292: RR 0.85, 95% CI 0.19 to 3.83; very low quality evidence).
- sequential intravenous then oral antibiotics compared with oral antibiotics (2 RCTs, n=506: RR 0.96, 95% CI 0.06 to 15.02; very low quality evidence).
- a single-dose injectable antibiotic then oral antibiotics compared with sequential intravenous then oral antibiotics (2 RCTs, n=225: RR 4.00, 95% CI 0.46 to 34.75; very low quality evidence).
- a single-dose injectable antibiotic then oral antibiotics compared with oral antibiotics (1 RCT, n=69: RR 1.37, 95% CI 0.33 to 5.68; very low quality evidence).

No evidence was presented in Pohl 2007 for safety or tolerability outcomes of oral antibiotics compared with injectable antibiotics.

4.3.2 Antibiotics in children

Choice of antibiotic

The systematic review by Strohmeier et al (2014) found no significant difference in gastrointestinal adverse effects between cephalosporins and other antibiotics (4

RCTs, n=591: RR 0.93, 95% CI 0.34 to 2.58; very low quality evidence). Discontinuation of treatment in 1 RCT was the same (4 children) in each group (1 RCT, n=461: RR 0.49, 95% CI 0.12 to 1.94; very low quality evidence). In a comparison of third generation cephalosporins compared with fourth generation cephalosporins there was no significant difference in the frequency of adverse events between groups (1 RCT, n=299: RR 1.12, 95% CI 0.76 to 1.63; very low quality evidence). Similarly there was no significant difference in total adverse events for a third generation cephalosporin compared with another third generation cephalosporin (ceftriaxone versus cefotaxime) (1 RCT, n=100: RR 0.67, 95% CI 0.12 to 3.82; very low quality evidence).

Frequency of antibiotic dosing

In the systematic review (Strohmeier et al. 2014) there was no significant difference in the number of children with hearing impairment (3 RCTs, n=271: RR 2.83, 95% CI 0.33 to 24.56; very low quality evidence) or kidney dysfunction (3 RCTs, n=419: RR 0.75, 95% CI 0.20 to 2.82; very low quality evidence) between different dosing frequencies of aminoglycosides (once daily or 8 hourly dosing).

Antibiotic course length

No systematic reviews or RCTs were identified in children that compared the safety and tolerability of different antibiotic course lengths.

Routes of antibiotic administration

The systematic review (Strohmeier et al. 2014) reported that of 4 RCTs of oral antibiotics compared with sequential intravenous and oral antibiotics, no adverse events were reported in 1 study and 1 further study did not report the outcome of adverse events. In the 2 RCTs that reported adverse events; 1 RCT found that 2 children in the oral antibiotic group were changed to intravenous treatment due to vomiting; in the other RCT 15 children had adverse effects with oral therapy and 3 in the injected antibiotic group but none required change in therapy (NICE analysis: RR 5.29, 95% CI 1.55 to 18.04, p=0.008); very low quality evidence).

Four of the 6 RCTs included in Strohmeier et al (2014) that assessed sequential short duration intravenous and oral antibiotics compared with longer duration intravenous antibiotics did not report adverse effects. The other 2 RCTs reported gastrointestinal upsets, but this did not significantly differ between groups (2 RCTs, RR 1.29 (0.55 to 3.05); very low quality evidence).

In the 1 RCT included in Strohmeier et al (2014) that compared a single dose of intramuscular antibiotic plus oral antibiotic with an oral antibiotic, there was no significant difference in total adverse events between groups (n=69: RR 1.37, 95% CI 0.33 to 5.68; very low quality evidence).

One RCT included in Strohmeier et al (2014) that compared oral ampicillin with ampicillin suppositories did not report any adverse event outcomes.

5 Antimicrobial resistance

The consumption of antimicrobials is a major driver for the development of antibiotic resistance in bacteria, and the 3 major goals of antimicrobial stewardship are to:

- optimise therapy for individual patients
- prevent overuse, misuse and abuse, and
- minimise development of resistance at patient and community levels.

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) recommends that the risk of antimicrobial resistance for individual patients and the population as a whole should be taken into account when deciding whether or not to prescribe an antimicrobial.

When antimicrobials are necessary to treat an infection that is not life-threatening, a narrow-spectrum antibiotic should generally be first choice. Indiscriminate use of broad-spectrum antibiotics creates a selective advantage for bacteria resistant even to these 'last-line' broad-spectrum agents, and also kills normal commensal flora leaving people susceptible to antibiotic-resistant harmful bacteria such as *C. difficile*. For infections that are not life-threatening, broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) need to be reserved for second-choice treatment when narrow-spectrum antibiotics are ineffective (CMO report 2011).

The English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report reported that antimicrobial consumption declined significantly between 2014 and 2015, with community prescribing from general and dental practice decreasing by more than 6%. Antibiotic prescribing in primary care in 2015 is at the lowest level since 2011, with broad-spectrum antibiotic use (antibiotics that are effective against a wide range of bacteria) continuing to decrease in primary care.

Urinary tract infections (UTIs) are most commonly caused by *E. coli* (recorded in more than half of all the mandatory surveillance reports for *E. coli* bacteraemia when foci of infection are reported). Better management of UTIs is seen as a potential intervention to reduce the incidence of *E. coli* bacteraemia. The ESPAUR report 2016 states that between 2010 and 2014 the rate of bloodstream infections caused by *E. coli* and *Klebsiella pneumoniae* increased by 15.6% and 20.8% respectively. Between 2014 and 2015 the number of cases continued to increase; *E. coli* bloodstream infections increased by a further 4.6% and K. pneumoniae increased by 9%.

The ESPAUR report 2016 notes that across England trimethoprim resistance in Gram-negative UTI ranges from 16.3% to 66.7%, with 86% of Clinical Commissioning Groups (CCGs) having resistance rates above 25%.

Antimicrobial resistance in included studies

Seven of the included RCTs contained information about antimicrobial resistance in acute pyelonephritis and complicated UTI in adults. No data were reported for children. None of the included studies were from the UK (see summary of included studies, section 2.2) and so the reported data should be interpreted with caution as resistance patterns vary by country and continent.

Resistance to quinolone antibiotics varied widely in 5 studies (0.4% to 56.9%), while the variation for resistance to cephalosporins was less (0% to 40%). Resistance to carbapenem antibiotics in 2 RCTs was found to be low (0% to 0.6%) conversely resistance to penicillin's was high (55.2% to 68%) except for a piperacillin-tazabactam in a single study (8.6%). Single RCTs reported resistance in a glycylcycline antibiotic (0%), an aminoglycoside antibiotic (18%) and co-trimoxazole (18.4%).

The presence of extended-spectrum β-lactamase (EBSL) producing *E. coli* was reported as accounting for 6.0% (11 of 182) of isolates in 1 RCT (Park et al. 2012) and EBSL producing *Enterobacteriaceae spp*. accounted for infection in 118 patients in another study (Wagenlehner et al. 2015). In one RCT (Peterson et al. 2008) more patients with complicated UTI had a treatment resistant Gram-negative pathogen (7.7%, 33 of 427) compared with those with acute pyelonephritis (2.1%, 4 of 192). The study also reported that 6 highly resistant Gram-positive pathogens (3 *Enterococcus faecalis* and 3 methicillin-resistant *Staphylococcus aureus* [MRSA]) were isolated in patients with complicated UTIs and 5 of the 6 were from subjects assigned to treatment with levofloxacin.

Five RCTs reported on resistance to quinolone antibiotics (levofloxacin or ciprofloxacin). One RCT (Wagenlehner et al. 2015) reported that in the microbiological modified intention to treat population for acute pyelonephritis 212 isolates (26.5%) had resistance to levofloxacin. An RCT from the year 2000 (Talan et al. 2000) found just 1 isolate resistant to ciprofloxacin (0.4%).The RCT by Pasiechnikov et al. (2015) in acute obstructive pyelonephritis found that 39 isolates (18.8%) were resistant to ciprofloxacin. In an RCT by Vazquez et al. (2008) 28 isolates (56.9%) of *E. coli*, were resistant to ciprofloxacin. The study by Park et al (2012) also reported resistance to ciprofloxacin in between to 14.3% to 30.1% of isolates in its study groups.

Five RCTs reported on resistance to cephalosporin antibiotics used in the study (ceftolozane-tazabactam, cephalothin, ceftriaxone, ceftazidime, and cefotaxime). One RCT (Wagenlehner et al. 2015) reported that 2.7% (20 of 731) isolates were resistant to ceftolozane-tazabactam. Data from an RCT in pregnant women with acute pyelonephritis (Moramezi et al. 2008) reported that resistance to cephalothin was found in 40% of isolates (number not reported). The authors also tested for resistance to ceftriaxone and found none, however in the RCT by Park et al (2012) ceftriaxone resistance was found in 6.2% (11 of 177) of isolates. One RCT (Vazquez et al. 2008) reported resistance in *E. coli* to cefotaxime (39.7%, 23 of 58) and ceftazidime (32.8%, 19 of 58). In one RCT of acute obstructive pyelonephritis (Pasiechnikov et al. 2015) resistance to ceftazidime was reported in 8.7% of isolates (n=18).

Two RCTs (Park et al. 2012 and Vazquez et al. 2012) reported on resistance to carbapenem antibiotics used in the study (imipenem-cilastatin and ertapenem). Resistance for these two antibiotics was low, 0% (0 of 58 isolates) resistance to imipenem (Vazquez et al. 2012) and 0.6% (1 of 58 isolates) resistance to ertapenem.

One RCT (Moramezi et al. 2008) used ampicillin in combination with gentamicin and reported that ampicillin resistance was high, 68% of isolates (number not reported), in pregnant women with acute pyelonephritis. Another RCT (Vazquez et al. 2012) reported that resistance to amoxicillin-clavulanate was also high (55.2%) with 32 of 58 isolates being not susceptible, however the trial also found that resistance to piperacillin (with tazobactam) was low (8.6%, 5 of 58).

Resistance to other antibiotics (tigecycline, gentamicin and co-trimoxazole) were addressed by single RCTs. Vazquez et al (2012) found no resistance to tigecycline (0 of 58 isolates). The RCT by Moramezi et al (2008) found gentamicin resistance in

18% of isolates (no number reported) and one RCT (Talan et al. 2000) reported that 47 isolates (18.4%) were resistant to co-trimoxazole.

6 Other considerations

6.1 Resource impact

6.1.1 Antibiotics

One RCT (Moramezi et al. 2008) in pregnant women with acute pyelonephritis found no significant difference in length of hospital stay in women taking ampicillin-gentamicin (n=60: mean reduction 4.8 hours, (p=0.22); very low quality evidence).

One RCT (Talan et al. 2000) which compared ciprofloxacin and co-trimoxazole in adult women with acute pyelonephritis found that resource use (hospital stay, visits and telephone contacts, laboratory tests and prescription costs) were higher in the co-trimoxazole group (no analysis reported). The only exception was for radiological procedures which was slightly higher in the ciprofloxacin group (no analysis reported). One systematic review (Eliakim-Raz et al. 2013) which compared durations of antibiotic treatment for acute pyelonephritis included the Talan et al. (2000) study and noted the shorter duration of stay in the short treatment arm (ciprofloxacin).

One RCT in the systematic review by Strohmeier et al (2014) on antibiotics for acute pyelonephritis in children found that with sequential intravenous then oral antibiotics versus longer duration (7 to 14 days) intravenous antibiotics the duration of hospital stay was lower (4.9 days) for the IV and oral group compared with 9.8 days for the IV therapy group.

Recommended antibiotics include nitrofurantoin, trimethoprim, penicillins, cephalosporins, quinolones and aminoglycosides. All are available as generic formulations, see Drug Tariff for costs.

Nitrofurantoin 25mg/5ml oral suspension is more expensive than other oral suspensions, such as trimethoprim 50mg/5ml. The cost of a 300 ml bottle of nitrofurantoin is £446.95 compared with £2.22 for a 100 ml bottle of trimethoprim (Drug Tariff, February 2018).

6.2 Medicines adherence

Medicines adherence may be a problem for some people with medicines that require frequent dosing (for example, some antibiotics) (NICE guideline on medicines adherence). Longer treatment durations for an acute illness (for example, for longer courses of antibiotics) may also cause problems with medicines adherence for some people.

7 Terms used in the guideline

Acute pyelonephritis in the included studies

One systematic review (Eliakim-Raz et al. 2013) and 1 randomised controlled trial (RCT; Ren et al. 2017) did not define any clinical or microbiological criteria for acute pyelonephritis. Among the 10 remaining included studies, all required a positive urine culture or presence of bacteriuria and fever as criteria. Additional criteria for the diagnosis of acute pyelonephritis varied among the studies.

Eight studies used the presence of pyuria; 6 studies used costovertebral angle pain or tenderness; 7 studies used flank pain or tenderness; 4 studies used dysuria; 3 studies used nausea or vomiting; 2 studies used raised laboratory values (raised white cell count; white blood cell casts in urine; C-reactive protein; erythrocyte sedimentation rate); 1 study used frequency or urgency; 1 study used suprapubic tenderness; 1 RCT in acute obstructive pyelonephritis used intravenous urogram; and 1 systematic review of acute pyelonephritis in children included studies that used CT and DMSA scans. One RCT described the presence of lower urinary tract infection (UTI) symptoms, but this was not defined.

Complicated urinary tract infection in the included studies

One systematic review (Eliakim-Raz et al. 2013) and 1 RCT (Ren et al. 2017) did not define any clinical or microbiological criteria for complicated UTI. Two systematic reviews (Strohmeier et al. 2014 and Kyriakidou et al. 2008) and 3 RCTs (Pasiechnikov et al. 2015; Moramezi et al. 2008 and Talan et al. 2000) excluded patients without acute pyelonephritis. Among the remaining 5 studies all required some form of existing bladder or kidney problem (for example, obstruction, neurogenic bladder, chronic or intermittent catheterisation, surgery or bladder instrumentation, renal tumour or fibrosis). Additional criteria for the diagnosis of complicated UTI varied among the studies.

Four studies used functional or anatomical urogenital tract abnormality; 3 studies used a positive urine culture or bacteriuria; 3 studies used pyuria; 2 studies used fever; 2 studies used costovertebral angle pain or tenderness; 2 studies used suprapubic pain or tenderness; 2 studies used nausea or vomiting; 2 studies used dysuria, frequency or urgency; 2 studies used urinary retention and 1 study used incontinence. 1 RCT used the term lower urinary tract symptoms (not defined).

Pyrexia

Raised temperature, generally above 38°C (100.4F), apyrexia is the absence of raised temperature.

Sepsis

A rare but serious complication of an infection see NHS choices.

Sequential antibiotic

An antibiotic that is initially given by intravenous injection or intramuscular injection that is changed to an oral antibiotic after a fixed period of days (usually 3 to 4 days), or after the cessation of fever.

Vesicoureteral reflux

An uncommon condition where urine leaks back up from the bladder into the ureters and kidneys; this occurs as a result of a problem with the valves in the ureters where they enter the bladder. The grading (grades I to V) depends upon the amount of reflux and dilation of the ureter and kidney.

Appendices

Appendix A: Evidence sources

Key area	Key question(s)	Evidence sources
Background	• What is the natural history of the infection? • What is the expected duration and severity of symptoms with or without antimicrobial treatment? • What are the most likely causative organisms? • What are the usual symptoms and signs of the infection? • What are the known complication rates of the infection, with and without antimicrobial treatment? • Are there any diagnostic or prognostic factors to identify people who may or may not benefit from an antimicrobial?	• European Association of Urology guidelines on urological infections 2017 • NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • NICE guideline NG63: Antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • NICE guideline CG54: Urinary tract infection in under 16s: diagnosis and management (updated 2017) • NICE Clinical knowledge summary on pyelonephritis • Frassetto 2015 • Kyriakidou et al. 2008 • Pasiechnikov et al. 2015 • Ren et al 2017 • Wagenlehner et al. 2015 • Moramezi et al. 2008 • Park et al. 2012 • Talan et al. 2000 • Vazquez et al. 2012
Safety netting	• What safety netting advice is needed for managing the infection?	• NICE guideline NG63: Antimicrobial stewardship: changing risk-related behaviours in the general population (2017)

Key area	Key question(s)	Evidence sources
Red flags	• What symptoms and signs suggest a more serious illness or condition (red flags)?	• NICE Clinical knowledge summary on pyelonephritis • NHS choices - kidney infection
Non-pharmacological interventions	• What is the clinical effectiveness and safety of non-pharmacological interventions for managing the infection or symptoms?	• Evidence review - see appendix F for included studies
Non-antimicrobial pharmacological interventions	• What is the clinical effectiveness and safety of non-antimicrobial pharmacological interventions for managing the infection or symptoms?	• Evidence review - see appendix F for included studies
Antimicrobial prescribing strategies	• What is the clinical effectiveness and safety of antimicrobial prescribing strategies (including back-up prescribing) for managing the infection or symptoms?	• Evidence review - see appendix F for included studies
Antimicrobials	• What is the clinical effectiveness and safety of antimicrobials for managing the infection or symptoms?	• Evidence review - see appendix F for included studies • NICE clinical knowledge summary on diarrhoea – antibiotic associated • British National Formulary (BNF) (December 2017)
	• Which people are most likely to benefit from an antimicrobial?	• Evidence review - see appendix F for included studies
	• Which antimicrobial should be prescribed if one is indicated (first, second and third line treatment, including people with drug allergy)?	• Evidence review - see appendix F for included studies
	• What is the optimal dose, duration and route of administration of antimicrobials?	• Evidence review - see appendix F for included studies • BNF (December 2017) • Summary of product characteristics
Antimicrobial resistance	• What resistance patterns, trends and levels of resistance exist both locally and nationally for the causative organisms of the infection	• Evidence review - see appendix F for included studies

Key area	Key question(s)	Evidence sources
	• What is the need for broad or narrow spectrum antimicrobials? • What is the impact of specific antimicrobials on the development of future resistance to that and other antimicrobials?	• European surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report (2016) • Chief medical officer (CMO) report (2011) • NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• Evidence review - see appendix F for included studies
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• Evidence review - see appendix F for included studies • NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)
Regulatory status	• What is the regulatory status of interventions for managing the infection or symptoms?	• Summary of product characteristics •

Appendix B: Review protocol

I	Review question	What pharmacological (antimicrobial and non-antimicrobial) and non-pharmacological interventions are effective in managing acute pyelonephritis and complicated urinary tract infections (UTIs)?	• antimicrobial includes antibiotics • non-antimicrobial includes analgesia • search will include terms for upper urinary tract infections, acute pyelonephritis and urosepsis
II	Types of review question	Intervention questions will primarily be addressed through the search.	These will, for example, also identify natural history in placebo groups and causative organisms in studies that use laboratory diagnosis, and relative risks of differing management options.
III	Objective of the review	To determine the effectiveness of prescribing and other management interventions in managing acute pyelonephritis and complicated urinary tract infections, in line with the major goals of antimicrobial stewardship. This includes interventions that lead prescribers to: • optimise outcomes for individuals • reduce overuse, misuse or abuse of antimicrobials. All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making.	The secondary objectives of the review of studies will include: • indications for prescribing an antimicrobial (for example 'red flags' and illness severity), thresholds for treatment and individual patient factors affecting antimicrobial choice • indications for no or delayed antimicrobial • indications for non-antimicrobial interventions • antimicrobial choice, optimal dose, duration (specifically length of treatment) and route for specified antimicrobial(s) • the natural history of the infection
IV	Eligibility criteria – population/	Population: Adults and children (aged 72 hours and older) with acute pyelonephritis or complicated UTI (or urosepsis) of any severity.	Subgroups of interest, those:

	disease/ condition/ issue/domain	Acute pyelonephritis is diagnosed in a person with a proven UTI who has loin pain and/or fever. A complicated UTI is an infection associated with a condition (for example, a structural or functional abnormality of the genitourinary tract) or an underlying disease, which increases the risk of a more serious outcome or treatment failure. Urosepsis is lower or upper UTI with systemic signs of sepsis. This review protocol includes acute pyelonephritis and complicated UTI in non-pregnant and pregnant women, men and children. Consideration will be given to differing management in subgroups based on age, gender, pregnancy, complicating factors and risk of resistance. Studies that use for example symptoms or signs (prognosis), clinical diagnosis or microbiological methods for diagnosing the condition.	• with protected characteristics under the Equality Act 2010. • with true allergy • pregnant women • men • children (possible age groups) • older people (frailty, care home resident, dementia) • people with 'complicated' UTI • people with risk factors[3] for increased resistance
V	Eligibility criteria – intervention(s)/ exposure(s)/ prognostic factor(s)	The review will include studies which include: • Non-pharmacological interventions[4] • Non-antimicrobial pharmacological interventions[5] • Antimicrobial pharmacological interventions[6]	Limited to those interventions commonly in use (as agreed by the committee)

3 Risk factors for increased resistance include: care home resident, recurrent UTI, previous hospitalisation, unresolving urinary symptoms, recent travel to country with increased resistance, previous UTI resistant to antibiotics (previous antibiotic use [trimethoprim]) (Source PHE management of infection guidance)

4 Non-pharmacological interventions include: no intervention, watchful waiting, delayed prescribing

5 Non-antimicrobial pharmacological interventions include: analgesics and NSAIDs

6 Antimicrobial pharmacological interventions include: delayed (back-up) prescribing, standby or rescue therapy, narrow or broad spectrum, single, dual or triple therapy, escalation or de-escalation of treatment. Antibiotics included in the search include those named in current guidance (plus the class to which they belong) plus other antibiotics agreed by the committee

		For the treatment of acute pyelonephritis and complicated UTI in primary, secondary or other care settings (for example walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example patient group direction).	
VI	Eligibility criteria – comparator(s)/ control or reference (gold) standard	Any other plausible strategy or comparator, including: • Placebo or no treatment. • Non-pharmacological interventions • Non-antimicrobial pharmacological interventions. • Antimicrobial pharmacological interventions	
VII	Outcomes and prioritisation	a) Clinical outcomes such as: • mortality • infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment) • time to clinical cure (mean or median time to resolution of illness) • reduction in symptoms (duration or severity) • rate of complications with or without treatment • safety, tolerability, and adverse effects. b) Thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials) c) Changes in antimicrobial resistance patterns, trends and levels as a result of treatment. d) Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction. e) Ability to carry out activities of daily living.	The committee have agreed that the following outcomes are critical: • reduction in symptoms (duration or severity) for example difference in time to substantial improvement • time to clinical cure (mean or median time to resolution of illness) • rate of complications[7] (including mortality) with or without treatment, including escalation of treatment • health and social care utilisation (including length of stay, ITU stays, planned and unplanned contacts). • thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials)

7 impaired renal function or renal failure, septicaemia, preterm labour in pregnancy, risk of blood infections (bacteraemia), renal abscess, renal scarring in children, neonatal sepsis. Risk of complications increased in severe illness (hypotension, tachycardia, reduced levels of consciousness, dehydration), age over 65 years, abnormalities of renal tract anatomy and function, foreign body within the renal tract, including renal stones and urinary, ureteric, or nephrostomy, immunocompromised, diabetes mellitus, pregnancy, persistent pyelonephritis despite treatment, renal impairment.

		f) Service user experience. g) Health and social care related quality of life, including long-term harm or disability. h) Health and social care utilisation (including length of stay, planned and unplanned contacts). The Committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important outcomes). Additionally, the Committee were asked to consider what clinically important features of study design may be important for this condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).	• an individual's risk factors for resistance and choice of antibiotic The committee have agreed that the following outcomes are important: • patient-reported outcomes, such as medicines adherence, patient experience • changes in antimicrobial resistance patterns, trends and levels as a result of treatment
VIII	Eligibility criteria – study design	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If insufficient evidence is available progress to: • Controlled trials • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Observational and cohort studies • Pre and post intervention studies (before and after) • Time series studies	Committee to advise the NICE project team on the inclusion of information from other condition specific guidance and on whether to progress due to insufficient evidence.
IX	Other inclusion exclusion criteria	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts • for antimicrobial resistance non-UK papers.	
X	Proposed sensitivity/ sub-group analysis, or meta-regression	The search may identify studies in population subgroups (for example adults, older adults, children (those aged under 18 years of age), and people with co-morbidities or characteristics that are protected under the Equality Act 2010 or in the NICE equality	

		impact assessment). These will be analysed within these categories to enable the production of management recommendations.	
XI	Selection process – duplicate screening/ selection/ analysis	All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above. A randomly selected initial sample of 10% of records will be screened by two reviewers independently. The rate of agreement for this sample will be recorded, and if it is over 90% then remaining references will screened by one reviewer only. Disagreement will be resolved through discussion. Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved. If large numbers of papers are identified and included at full text, the Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes.	
XII	Data management (software)	Data management will be undertaken using EPPI-reviewer software. Any pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). ‘GRADEpro’ will be used to assess the quality of evidence for each outcome.	
XIII	Information sources – databases and dates	Medline; Medline in Process; Embase; Cochrane database of systematic reviews (CDSR); Database of abstracts of effectiveness (DARE) (legacy); Cochrane Central Register of Controlled Trials (CENTRAL); Health Technology Assessment (HTA) database; Clinicaltrials.gov • All the above to be searched from 2006 to present day. • Filters for systematic reviews, RCTs and comparative studies to be applied, unless numbers without filters are low • Searches to be limited to studies reported in English. • Animal studies and conference abstracts to be excluded Medicines and Healthcare products Regulatory Agency (MHRA) website; European Medicines Agency (EMA) website; U.S. Food and Drug Administration (FDA) website; Drug Tariff; MIMs • The above to be searched for advice on precautions, warnings, undesirable effects of named antimicrobials.	

XIV	Identify if an update	Not applicable at this time.	
XV	Author contacts	Web: https://www.nice.org.uk/guidance/indevelopment/gid-apg10003 Email: infections@nice.org.uk	
XVI	Highlight if amendment to previous protocol	For details please see the interim process guide (2017).	
XVII	Search strategy – for one database	For details see appendix C of the full guideline.	
XVIII	Data collection process – forms/ duplicate	GRADE profiles will be used, for details see appendix H of the full guideline.	
XIX	Data items – define all variables to be collected	GRADE profiles will be used, for details see appendix H of the full guideline.	
XX	Methods for assessing bias at outcome/study level	Standard study checklists will be used to critically appraise individual studies. For details please see the interim process guide (2017). The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/	
XXI	Criteria for quantitative synthesis (where suitable)	For details please see the interim process guide (2017).	
XXII	Methods for analysis – combining studies and exploring (in)consistency	For details please see the interim process guide (2017).	

XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see the interim process guide (2017).	
XXIV	Assessment of confidence in cumulative evidence	For details please see the interim process guide (2017).	
XXV	Rationale/ context – Current management	For details please see the introduction to the evidence review in the guideline.	
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with the interim process guide (2017). Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.	
XXVII	Sources of funding/support	Developed and funded by NICE.	
XXVIII	Name of sponsor	Developed and funded by NICE.	
XXIX	Roles of sponsor	NICE funds and develops guidelines for those working in the NHS, public health, and social care in England.	

Appendix C: Literature search strategy

1 Search format

The search strategy has been designed to cover four UTI protocols and it takes the following format:

Urinary Tract Infections

AND (Named Antibiotics OR Classes of Antibiotics OR Pain Relief OR NSAIDs OR Cranberry Products OR Alkalinising agents OR Bladder instillations OR Drinking Fluids OR Prescribing Strategies OR Self Care OR Catheter Removal)

AND (Systematic Reviews OR Randomised Controlled Trials OR Observational Studies)

AND Limits

Note there is an additional search in this format:

Named Antibiotics AND Drug Resistance AND Limits

2 Overview of search results

	No. of hits in MEDLINE	Position in the strategy
Search without any limits	65,619	Line 178
Search with limits	14,263	Line 184
Search with limits and Systematic Reviews	2,428	Line 200
Search with limits and RCTs (not SRs)	2,230	Line 217
Search with limits and Observational Studies (not SRs or RCTs)	3,795	Line 240
Search with limits (without SRs, RCTs, Observational)	5,810	Line 241
Named Antibiotics AND Drug Resistance	48,201	Line 257
Named Antibiotics AND Drug Resistance with Limits	20,072	Line 262

3 Contents of the search strategy

Main concepts	Coverage	Position in strategy
Urinary Tract Infections	Urinary tract infections Cystitis Vesico-ureteral reflux Pyelonephritis Catheter-Related Infections Bacteriuria Urosepsis Urethritis	Lines 1-20
Named Antibiotics	Trimethoprim Nitrofurantoin Fosfomycin Methenamine hippurate Gentamicin Amikacin Tobramycin Amoxicillin Ampicillin Co-amoxiclav Pivmecillinam	Lines 21-84

	Cefalexin Cefotaxime Cefixime Ceftriaxone Ciprofloxacin Ofloxacin Colistin Ertapenem Doxycycline Septrin Chloramphenicol Tazocin Aztreonam Temocillin Tigecycline Vancomycin Teicoplanin Linezolid Cefuroxime Cefradine Ceftazidime Levofloxacin	
Classes of Antibiotics	Aminoglycosides Penicillins Cephalosporins Quinolones Carbapenems Tetracyclines	Lines 86-93
Pain Relief	Paracetamol Ibuprofen Naproxen Codeine Diclofenac Analgesics Non-steroidal anti-inflammatory drugs	Lines 96-111
Non-pharmaceutical products	Cranberry products Barley products D-Mannose	Lines 113-119
Alkalinising agents	Potassium citrate Sodium citrate Sodium bicarbonate	Lines 121-127
Bladder instillations	Chlorhexidine solution Sodium chloride solution	Lines 129-133
Drinking Fluids	Fluid therapy Drinking water, beverages, fluids or liquids	Lines 135-139
Prescribing Strategies	Watchful waiting No intervention Active surveillance Delayed treatment Prescribing times Antibiotic prophylaxis	Lines 141-160
Self Care	Self management Self care secondary prevention Catheter removal	Lines 162-176
Systematic Reviews	Meta analysis Systematic Reviews Reviews	Lines 185-199
Randomised Controlled Trials	RCTs Controlled Clinical Trials	Lines 201-215

	Cross over studies	
Observational Studies	Observational Study Epidemiologic Studies Case-Control Studies Cohort Studies Cross-Sectional Studies Controlled Before-After Studies	Lines 218-238
Limits	2006-Current Exclude Animal studies Exclude letters, editorials and letters	Lines 179-184
Additional search	Drug resistance	Lines 242-262

4 Key to search operators

/	Medical Subject Heading (MeSH) term
Exp	Explodes the MeSH terms to retrieve narrower terms in the hierarchy
.ti	Searches the title field
.ab	Searches the abstract field
*	Truncation symbol (searches all word endings after the stem)
adj*n*	Adjacency operator to retrieve records containing the terms within a specified number (*n*) of words of each other

5 Search strategy for MEDLINE

Database(s): **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	exp urinary tract/	406398
2	exp urinary tract infections/	42175
3	exp cystitis/	8814
4	vesico-ureteral reflux/	7753
5	exp pyelonephritis/	14154
6	exp Urinary Calculi/	32650
7	Urethritis/	4483
8	Catheters, Indwelling/	17219
9	Urinary Catheters/	530
10	Urinary Catheterization/	13329
11	Catheter-Related Infections/	3344
12	Catheter Obstruction/	139
13	(UTI or CAUTI or RUTI or cystitis* or bacteriuria* or pyelonephriti* or pyonephrosi* or pyelocystiti* or pyuri* or VUR or urosepsis* or uroseptic* or urosepses* or urethritis*).ti,ab.	38919
14	((urin* or renal* or kidney*) adj1 (system* or tract* or calculus or calculi* or stone* or sepsis*)).ti,ab.	82884

15	((bladder* or genitourin* or genito urin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj3 (infect* or bacteria* or microbial* or block* or obstruct* or catheter* or inflamm*)).ti,ab.	87091
16	((upper or lower) adj3 urin*).ti,ab.	21980
17	(bladder* adj3 (ulcer* or ulcus)).ti,ab.	151
18	(schistosomiasis adj3 (haematobia or hematobia or urin*)).ti,ab.	966
19	((vesicorenal* or vesicoureteral* or vesicoureteric* or vesico renal* or vesico ureteral* or vesico ureteric* or bladder* or cystoureteral* or ureter* or urether* or nephropathy*) adj3 (backflow* or reflux*)).ti,ab.	7989
20	or/1-19	576113
21	Trimethoprim/	6280
22	(Trimethoprim* or Monotrim*).ti,ab.	14565
23	Nitrofurantoin/	2517
24	(Nitrofurantoin* or Genfura* or Macrobid*).ti,ab.	2980
25	Fosfomycin/	1685
26	(Fosfomycin* or Phosphomycin* or Fosfocina* or Monuril* or Monurol* or Fomicyt*).ti,ab.	2378
27	Methenamine/	1045
28	(Methenamine* or hexamine* or hippurate* or Hiprex*).ti,ab.	2411
29	Gentamicins/	17268
30	(Gentamicin* or Cidomycin*).ti,ab.	21976
31	Amikacin/	3751
32	(amikacin* or Amikin*).ti,ab.	8118
33	Tobramycin/	3973
34	(tobramycin* or Nebcin*).ti,ab.	6203
35	Amoxicillin/	8654
36	(Amoxicillin* or Amoxil*).ti,ab.	12541
37	Ampicillin/	12932
38	ampicillin*.ti,ab.	20478
39	Amoxicillin-Potassium Clavulanate Combination/	2301
40	(co-amoxiclav* or Coamoxiclav* or Amox-clav* or Amoxicillin-Clavulanic Acid* or Amoxicillin-Potassium Clavulanate Combination* or Amoxi-Clavulanate* or Clavulanate Potentiated Amoxycillin Potassium* or Clavulanate-Amoxicillin Combination* or Augmentin*).ti,ab.	13396
41	Amdinocillin Pivoxil/	205
42	(pivmecillinam* or Pivamdinocillin* or Selexid*).ti,ab.	268

43	Cefalexin/	1974
44	(Cefalexin* or Cephalexin* or Keflex*).ti,ab.	2605
45	Cefotaxime/	5101
46	cefotaxime*.ti,ab.	7488
47	Cefixime/	711
48	(cefixime* or Suprax*).ti,ab.	1438
49	Ceftriaxone/	5210
50	(ceftriaxone* or Rocephin*).ti,ab.	8834
51	Ciprofloxacin/	11578
52	(Ciprofloxacin* or Ciproxin*).ti,ab.	21632
53	Ofloxacin/	5795
54	(ofloxacin* or Tarivid*).ti,ab.	6236
55	Colistin/	3071
56	(Colistin* or Colistimethate* or Colimycin* or Coly-Mycin* or Colymycin* or Colomycin* or Promixin*).ti,ab.	4291
57	(Ertapenem* or Invanz*).ti,ab.	1135
58	Doxycycline/	8515
59	(Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab.	11268
60	Trimethoprim, Sulfamethoxazole Drug Combination/	6306
61	(Septrin* or Co-trimoxazole* or Cotrimoxazole* or Sulfamethoxazole Trimethoprim Comb* or Trimethoprim Sulfamethoxazole Comb*).ti,ab.	5497
62	Chloramphenicol/	18958
63	(Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab.	24993
64	Piperacillin/	2423
65	(Tazocin* or Piperacillin* or Tazobactam*).ti,ab.	6222
66	Aztreonam/	1336
67	(Aztreonam* or Azactam*).ti,ab.	2743
68	(Temocillin* or Negaban*).ti,ab.	237
69	(Tigecycline* or Tygacil*).ti,ab.	2337
70	Vancomycin/	11836
71	(Vancomycin* or Vancocin*).ti,ab.	22446
72	Teicoplanin/	2067
73	(Teicoplanin* or Targocid*).ti,ab.	3233
74	Linezolid/	2421

75	(Linezolid* or Zyvox*).ti,ab.	4568
76	Cefuroxime/	2037
77	(Cefuroxime* or Cephuroxime* or Zinacef* or Zinnat* or Aprokam*).ti,ab.	3919
78	Cefradine/	540
79	(Cefradine* or Cephradine* or Nicef*).ti,ab.	699
80	Ceftazidime/	3461
81	(Ceftazidime* or Fortum* or Tazidime*).ti,ab.	7727
82	Levofloxacin/	2708
83	(Levofloxacin* or Evoxil* or Tavanic*).ti,ab.	6119
84	or/21-83	214218
85	20 and 84	18255
86	exp aminoglycosides/	142346
87	exp penicillins/	76761
88	exp cephalosporins/	39233
89	exp quinolones/	41144
90	exp Carbapenems/	8711
91	exp Tetracyclines/	44511
92	(Aminoglycoside* or Penicillin* or Cephalosporin* or Quinolone* or Carbapenem* or Tetracycline*).ti,ab.	120900
93	or/86-92	359234
94	20 and 93	22544
95	Anti-Infective Agents, Urinary/	2557
96	Acetaminophen/	15854
97	(paracetamol* or acetaminophen* or Panadol* or perfalgan* or calpol*).ti,ab.	20775
98	Ibuprofen/	7581
99	(ibuprofen* or arthrofen* or ebufac* or rimafen* or brufen* or calprofen* or feverfen* or nurofen* or orbifen*).ti,ab.	11191
100	Naproxen/	3730
101	(Naproxen* or Naprosyn* or Stirlescent*).ti,ab.	5450
102	Codeine/	4237
103	(codeine* or Galcodine*).ti,ab.	4407
104	Diclofenac/	6823
105	(Diclofenac* or Voltarol* or Dicloflex* or Econac* or Fenactol* or Volsaid* or Enstar* or Diclomax* or Motifene* or Rhumalgan* or Pennsaid*).ti,ab.	9698

106	(nsaid* or analgesic*).ti,ab.	87160
107	((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).ti,ab.	34162
108	analgesics/	43460
109	exp analgesics, non-narcotic/	299959
110	analgesics, short-acting/	8
111	or/96-110	400073
112	20 and 111	10492
113	Vaccinium macrocarpon/	645
114	(cranberry* or cranberries* or vaccinium macrocarpon*).ti,ab.	1247
115	Hordeum/	8153
116	(barley* or hordeum*).ti,ab.	15407
117	Mannose/	8489
118	(mannose* or d-mannose* or dmannose*).ti,ab.	24493
119	or/113-118	45484
120	20 and 119	1500
121	potassium citrate/	245
122	(potassium citrate* or Effercitrate*).ti,ab.	546
123	(sodium citrate* or Cymalon* or Cystocalm* or Micolette* or Micralax*).ti,ab.	2644
124	sodium bicarbonate/	4205
125	(sodium bicarbonate* or S-Bicarb* or SodiBic* or Thamicarb* or Polyfusor*).ti,ab.	5477
126	((alkalizer* or alkalinisation* or alkalinization* or alkalinising or alkalinizing) adj3 (drug* or agent* or therap*)).ti,ab.	191
127	or/121-126	10890
128	20 and 127	1049
129	Chlorhexidine/	7123
130	((chlorhexidine or sodium chloride*) adj3 (solution* or diluent* or instillation* or intravesical*)).ti,ab.	3327
131	Administration, Intravesical/	3418
132	(bladder* adj3 (instillat* or drug admin*)).ti,ab.	540
133	or/129-132	13618
134	20 and 133	1976
135	Drinking/ or Drinking Behavior/	19308
136	Fluid therapy/	17515
137	exp Beverages/	114331

138	((water* or fluid* or liquid* or beverage* or drinks) adj3 (consumption* or consume* or consuming* or intake* or drink* or hydrat* or rehydrat*)).ti,ab.	80871
139	or/135-138	210996
140	20 and 139	6845
141	watchful waiting/	2278
142	Antibiotic Prophylaxis/	11779
143	"no intervention*".ti,ab.	6125
144	(watchful* adj2 wait*).ti,ab.	2077
145	(wait adj2 see).ti,ab.	1225
146	(active* adj2 surveillance*).ti,ab.	5705
147	(expectant* adj2 manage*).ti,ab.	2738
148	((prescription* or prescrib*) adj4 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or postcoital* or postcoitus* or postsex* or postintercourse* or post coital* or post coitus* or post sex* or post intercourse* or night* or nocturnal* or prophylaxis* or prophylactic* or prevent* or preoperative* or pre operative* or perioperative* or peri operative* or postoperative* or post operative*)).ti,ab.	25168
149	((misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*) adj4 (bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*")).ti,ab.	1761
150	((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab.	26341
151	or/141-150	82704
152	anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/	844581
153	(antibacter* or anti-bacter* or antibiot* or anti-biot* or antimicrobial* or anti-microbial*).ti,ab.	401551
154	152 or 153	1017858
155	(postcoital* or postcoitus* or postsex* or postintercourse* or post coital* or post coitus* or post sex* or post intercourse* or night* or nocturnal* or delay* or defer* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or (prescribing adj strateg*) or "red flag*" or prevent* or prophylaxis* or prophylactic*).ti,ab.	4758691
156	Coitus/	6880
157	Inappropriate prescribing/	1695
158	or/155-157	4764914
159	154 and 158	221871
160	151 or 159	292655

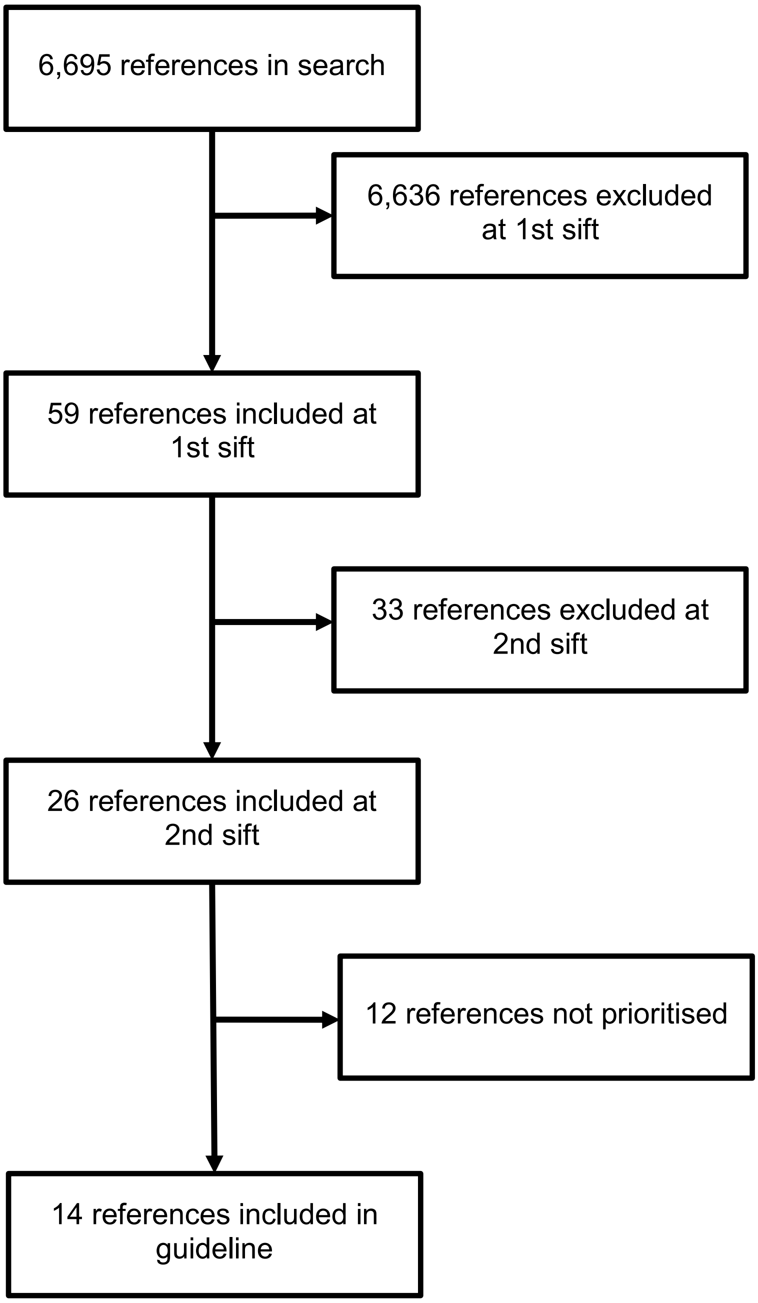
161	20 and 160	15345
162	Self Care/ or self medication/	32883
163	((self or selves or themsel*) adj4 (care or manag*)).ti,ab.	33223
164	Secondary Prevention/	17180
165	Hygiene/	14900
166	Baths/	4966
167	Soaps/	2343
168	((postcoital* or postcoitus* or postsex* or postintercourse* or post coital* or post coitus* or post sex* or post intercourse* or postmicturit* or micturit* or postmicturat* or micturat* or urinat* or defecat* or toilet* or lavatory or lavatories or perineal* or perineum*) adj3 (prophylaxis* or prophylactic* or treatment* or wipe* or wiping or hygiene* or hygienic* or clean* or douche* or douching* or bath* or soap* or wash* or shower*)).ti,ab.	1611
169	(second* adj3 prevent*).ti,ab.	21506
170	or/162-169	112930
171	20 and 170	1919
172	or/8-10	29047
173	Device Removal/	10427
174	172 and 173	753
175	(Catheter* adj3 (care* or removal* or removing* or remove* or "take* out" or "taking out" or change* or changing* or clean* or wash* or bath* or hygiene* or hygienic*)).ti,ab.	10138
176	174 or 175	10561
177	20 and 176	5423
178	85 or 94 or 95 or 112 or 120 or 128 or 134 or 140 or 161 or 171 or 177	65619
179	limit 178 to yr="2006 -Current"	21429
180	limit 179 to english language	19392
181	Animals/ not (Animals/ and Humans/)	4291504
182	180 not 181	15047
183	limit 182 to (letter or historical article or comment or editorial or news)	784
184	182 not 183	14263
185	Meta-Analysis.pt.	74747
186	Meta-Analysis as Topic/	15461
187	Network Meta-Analysis/	34
188	Review.pt.	2230816
189	exp Review Literature as Topic/	9193

190	(metaanaly* or metanaly* or (meta adj3 analy*)).ti,ab.	109466
191	(review* or overview*).ti.	389897
192	(systematic* adj5 (review* or overview*)).ti,ab.	109630
193	((quantitative* or qualitative*) adj5 (review* or overview*)).ti,ab.	7343
194	((studies or trial*) adj2 (review* or overview*)).ti,ab.	36022
195	(integrat* adj3 (research or review* or literature)).ti,ab.	8769
196	(pool* adj2 (analy* or data)).ti,ab.	22123
197	(handsearch* or (hand adj3 search*)).ti,ab.	7550
198	(manual* adj3 search*).ti,ab.	4715
199	or/185-198	2487695
200	184 and 199	2428
201	Randomized Controlled Trial.pt.	448607
202	Controlled Clinical Trial.pt.	91938
203	Clinical Trial.pt.	508233
204	exp Clinical Trials as Topic/	304614
205	Placebos/	34193
206	Random Allocation/	89847
207	Double-Blind Method/	143336
208	Single-Blind Method/	23779
209	Cross-Over Studies/	40867
210	((random* or control* or clinical*) adj3 (trial* or stud*)).ti,ab.	1003782
211	(random* adj3 allocat*).ti,ab.	28603
212	placebo*.ti,ab.	189958
213	((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).ti,ab.	153095
214	(crossover* or (cross adj over*)).ti,ab.	74298
215	or/201-214	1721840
216	184 and 215	2933
217	216 not 200	2230
218	Observational Studies as Topic/	1959
219	Observational Study/	31517
220	Epidemiologic Studies/	7369
221	exp Case-Control Studies/	834068
222	exp Cohort Studies/	1623327
223	Cross-Sectional Studies/	234990

224	Controlled Before-After Studies/	218
225	Historically Controlled Study/	97
226	Interrupted Time Series Analysis/	243
227	Comparative Study.pt.	1770190
228	case control*.ti,ab.	102767
229	case series.ti,ab.	52479
230	(cohort adj (study or studies)).ti,ab.	133481
231	cohort analy*.ti,ab.	5462
232	(follow up adj (study or studies)).ti,ab.	43245
233	(observational adj (study or studies)).ti,ab.	70390
234	longitudinal.ti,ab.	186074
235	prospective.ti,ab.	454707
236	retrospective.ti,ab.	381342
237	cross sectional.ti,ab.	245513
238	or/218-237	3929955
239	184 and 238	5469
240	239 not (200 or 216)	3795
241	184 not (200 or 216 or 240)	5810
242	exp Drug Resistance, Bacterial/	72249
243	exp Drug Resistance, Multiple/	28752
244	((bacter* or antibacter* or anti-bacter* or "anti bacter*") adj4 (resist* or tolera*)).ti,ab.	34156
245	((antibiot* or anti-biot* or "anti biot*") adj4 (resist* or tolera*)).ti,ab.	42316
246	(multi* adj4 drug* adj4 (resist* or tolera*)).ti,ab.	12134
247	(multidrug* adj4 (resist* or tolera*)).ti,ab.	38335
248	(multiresist* or multi-resist* or "multi resist*").ti,ab.	6214
249	((microb* or antimicrob* or anti-microb* or "anti microb*") adj4 (resist* or tolera*)).ti,ab.	22368
250	(superbug* or super-bug* or "super bug*").ti,ab.	448
251	Superinfection/	1644
252	(superinvasion* or super-invasion* or "super invasion*" or superinfection* or super-infection* or "super infection*").ti,ab.	5185
253	R Factors/	4157
254	"r factor*".ti,ab.	3648
255	(resist* factor* or "r plasmid*" or resist* plasmid*).ti,ab.	5218
256	or/242-255	180317

257	84 and 256	48201
258	limit 257 to yr="2006 -Current"	25203
259	limit 258 to english language	23256
260	259 not 181	20939

Appendix D: Study flow diagram



Appendix E: Evidence prioritisation

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Which antibiotic is most effective?				
Antibiotics versus different antibiotics	Strohmeier et al. 2014	Armstrong et al. 2016 Huntington et al. 2016 Moramezi et al. 2008 Park et al. 2012 Pasiechnikov et al. 2015 Peterson et al. 2008 Talan et al. 2000 Vazquez et al. 2012 Wagenlehner et al. 2015	Coats et al. 2013 Hodson et al. 2007 Golan et al. 2015 Neumann et al. 2011 Singh et al. 2013	Ebrahimzadeh et al. 2010 Hewitt et al. 2008 Klausner et al. 2007 Montini et al. 2007 Neuhaus et al. 2008 Klausner et al. 2007 Monmaturapoj et al. 2012
What is the optimal dosage, duration and route of administration of antibiotic?				
Dosage	-	-	-	-
Frequency of dosing	Strohmeier et al. 2014			
Duration	Eliakim-Raz et al. 2013 Kyriakidou et al. 2008 Strohmeier et al. 2014	Ren et al. 2017	Coats et al. 2013	Sandberg et al. 2012
Route of administration	Pohl 2010 Strohmeier et al. 2014		Neumann et al. 2011	Bocquet et al. 2012

[1] See appendix F for full references of included studies
[2] See appendix I for full references of not-prioritised studies, with reasons for not prioritising these studies

Appendix F:Included studies

Armstrong ES, Mikulca JA, Cloutier DJ et al. (2016) Outcomes of high-dose levofloxacin therapy remain bound to the levofloxacin minimum inhibitory concentration in complicated urinary tract infections. BMC infectious diseases 16(1), 710

Eliakim-Raz N, Yahav D, Paul M et al. (2013) Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection-- 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. The Journal of antimicrobial chemotherapy 68(10), 2183-91

Huntington JA, Sakoulas G, Umeh O et al. (2016) Efficacy of ceftolozane/tazobactam versus levofloxacin in the treatment of complicated urinary tract infections (cUTIs) caused by levofloxacinresistant pathogens: Results from the ASPECT-cUTI trial. Journal of Antimicrobial Chemotherapy 71(7), 2014-2021

Kyriakidou KG, Rafailidis P, Matthaiou DK et al. (2008) Short- versus long-course antibiotic therapy for acute pyelonephritis in adolescents and adults: a meta-analysis of randomized controlled trials. Clinical therapeutics 30(10), 1859-68

Moramezi F, Barati M, Masihi S (2008) Comparison between cephalothin and ampicillin + gentamicin in treatment of pyelonephritis in pregnancy. Pakistan Journal of Medical Sciences 24(6), 865-868

Park DW, Peck KR, Chung MH et al. (2012) Comparison of ertapenem and ceftriaxone therapy for acute pyelonephritis and other complicated urinary tract infections in Korean adults: a randomized, double-blind, multicenter trial. Journal of Korean medical science 27(5), 476-83

Pasiechnikov S, Buchok O, Sheremeta R et al. (2015) Empirical treatment in patients with acute obstructive pyelonephritis. Infectious disorders drug targets 15(3), 163-70

Peterson J, Kaul S, Khashab M et al. (2008) A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. Urology 71(1), 17-22

Pohl A (2007) Modes of administration of antibiotics for symptomatic severe urinary tract infections. The Cochrane database of systematic reviews (4), CD003237

Ren H, Li X, Ni Z-H et al. (2017) Treatment of complicated urinary tract infection and acute pyelonephritis by short-course intravenous levofloxacin (750 mg/day) or conventional intravenous/oral levofloxacin (500 mg/day): prospective, open-label, randomized, controlled, multicenter, non-inferiority clinical trial. International urology and nephrology, 49; 499-507

Strohmeier Y, Hodson EM, Willis NS et al. (2014) Antibiotics for acute pyelonephritis in children. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD003772. DOI: 10.1002/14651858.CD003772.pub4.

Talan DA, Stamm WE, Hooton TM et al. (2000) Comparison of Cirpofloxacin (7 days) and Trimethoprim-Sulfamethoxazole (14 days) for Acute Uncomplicated Pyelonephritis in Women: A Randomized Trial. JAMA 283 (12), 1583-90

Vazquez JA, Gonzalez P, Luis D et al . (2012) Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. Current medical research and opinion 28(12), 1921-31

Wagenlehner FM, Umeh O, Steenbergen J et al. (2015) Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). The Lancet 385: 1949-56

Appendix G: Quality assessment of included studies

G.1 Antimicrobials

Table 2: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Eliakim-Raz N et al (2013)	Kyriakidou KG et al (2008)	Pohl A (2007)	Strohmeier Y et al. (2014)
Did the review address a clearly focused question?	Yes	Yes	Yes	Yes
Did the authors look for the right type of papers?	Yes	Yes	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Yes	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes[a]	Yes[b]	Yes[a]	Yes[a]
If the results of the review have been combined, was it reasonable to do so?	Yes[c]	Unclear[d]	Yes	Yes
What are the overall results of the review?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise are the results?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
Can the results be applied to the local population?	Yes	Yes	Yes	Yes
Were all important outcomes considered?	Yes	No[f]	Yes	No[g]
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles

Table 3: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	ASPECT-cUTI[a]	Moramezi F et al (2008)	Park DW et al (2012)	Pasiechnikov et al (2015)	Peterson J et al (2008)	Ren H et al (2017)	Talan DA et al (2000)	Vazquez JA et al (2012)
Did the trial address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Unclear[b]	Yes	Unclear[b]	Yes	Unclear[b]	Unclear[b]	Yes
Were patients, health workers and study personnel blinded?	Yes	No[c]	Yes	No[c]	Yes	No[g]	Yes	Yes
Were the groups similar at the start of the trial?	Yes	Unclear[d]	Yes	Unclear[d]	Yes	Yes	Unclear[h]	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes	Yes	No[i]	Yes	Yes	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Unclear[e]	Yes	Yes	Yes	Yes	Yes	Yes
How large was the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were all clinically important outcomes considered?	Yes	No[f]	Yes	Yes	Yes	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles

Study reference	ASPECT-cUTI[a]	Moramezi F et al (2008)	Park DW et al (2012)	Pasiechnikov et al (2015)	Peterson J et al (2008)	Ren H et al (2017)	Talan DA et al (2000)	Vazquez JA et al (2012)

[a] Includes papers by Wagenlehner FM et al. 2015; Armstrong ES et al. 2016; Huntington JA et al. 2016
[b] The authors state that the participants were randomised by the method of randomisation is not described
[c] Blinding is not discussed by the authors
[d] No details or little detail of the baseline characteristics of the participants are provided
[e] Details of the numbers of patients at follow-up are not provided
[f] Safety and adverse event outcomes not reported
[g] The authors report that this was an open-label study
[h] More women in the Trimethoprim-Sulfamethoxazole group had bacteraemia (8%) than in the Ciprofloxacin group (4%) but it is unclear if this is statistically significant
[i] As well as antibiotic therapy patients were also randomised to a particular surgical intervention (percutaneous nephrostomy or ureteral stenting)

Appendix H: GRADE profiles

H.1 Antimicrobials for acute pyelonephritis and complicated urinary tract infection in adults

Table 4: GRADE profile – ceftolozane-tazabactam versus levofloxacin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftolozane/ tazabactam	Levofloxacin	Relative (95% CI)	Absolute		
Composite cure[1] at 5 to 9 days after treatment (clinical cure and microbiological eradication in the modified intention to treat (ITT) population[2])												
1[3]	randomised trials	serious risk of bias[4]	not applicable	no serious indirectness	no serious imprecision	none	306/398 (76.9%)	275/402 (68.4%)	% difference 8.5 (2.3 to 14.6) NICE analysis: RR 1.12 (1.03 to 1.22)	82 more per 1000 (from 21 more to 150 more)	⊕⊕⊕O MODERATE	CRITICAL
Microbiological eradication[1] at 5 to 9 days after treatment (in the modified intention to treat (ITT) population)												
1[3]	randomised trials	serious risk of bias[4]	not applicable	no serious indirectness	no serious imprecision	none	320/398 (80.4%)	290/402 (72.1%)	% difference 8.3 (2.4 to 14.1) NICE analysis: RR 1.11 (1.03 to 1.20)	79 more per 1000 (from 22 more to 144 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical cure[1] at 5 to 9 days (in the modified intention to treat (ITT) population)												
1[3]	randomised trials	serious risk of bias[4]	not applicable	no serious indirectness	no serious imprecision	none	366/398 (92%)	356/402 (88.6%)	% difference 3.4 (-0.7 to 7.6) NICE analysis: RR 1.04 (0.99 to 1.09)	35 more per 1000 (from 9 fewer to 80 more)	⊕⊕⊕O MODERATE	CRITICAL
Composite cure[1] at 5 to 9 days (clinical cure and microbiological eradication in the modified intention to treat (ITT) population with complicated lower urinary tract infection)												
1[3]	randomised trials	serious risk of bias[4]	not applicable	no serious indirectness	serious[5]	none	47/70 (67.1%)	35/74 (47.3%)	% difference 19.8 (3.7 to 34.6) NICE analysis: RR 1.42 (1.06 to 1.90)	199 more per 1000 (from 28 more to 426 more)	⊕⊕OO LOW	CRITICAL
Composite cure[1] at 5 to 9 days (clinical cure and microbiological eradication in the modified intention to treat (ITT) population with pyelonephritis)												
1[3]	randomised trials	serious risk of bias[4]	not applicable	no serious indirectness	no serious imprecision	none	259/328 (79%)	240/328 (73.2%)	% difference 5.8 (-0.7 to 12.3) NICE analysis: RR 1.08 (0.99 to 1.18)	59 more per 1000 (from 7 fewer to 132 more)	⊕⊕⊕O MODERATE	CRITICAL
Composite cure[1] at 5 to 9 days (clinical cure and microbiological eradication in the modified intention to treat (ITT) population under 65 years)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftolozane/ tazabactam	Levofloxacin	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious risk of bias[4]	not applicable	no serious indirectness	no serious imprecision	none	236/298 (79.2%)	222/303 (73.3%)	% difference 5.9 (-0.9 to 12.7) NICE analysis: RR 1.08 (0.99 to 1.18)	59 more per 1000 (from 7 fewer to 132 more)	⊕⊕⊕O MODERATE	CRITICAL
Composite cure[1] at 5 to 9 days (clinical cure and microbiological eradication in the modified intention to treat (ITT) population over 65 years)												
1[3]	randomised trials	serious risk of bias[4]	not applicable	no serious indirectness	serious[5]	none	70/100 (70%)	53/99 (53.5%)	% difference 16.5 (3 to 29.2) NICE analysis: RR 1.31 (1.05 to 1.64)	166 more per 1000 (from 27 more to 343 more)	⊕⊕OO LOW	CRITICAL
Composite cure[1] at 5 to 9 days (clinical cure and microbiological eradication in the modified intention to treat (ITT) population without bacteraemia)												
1[3]	randomised trials	serious risk of bias[4]	not applicable	no serious indirectness	serious[5]	none	283/369 (76.7%)	256/369 (69.4%)	% difference 7.3 (0.9 to 13.6) NICE analysis: RR 1.11 (1.01 to 1.21)	76 more per 1000 (from 7 more to 146 more)	⊕⊕OO LOW	CRITICAL
Composite cure[1] at 5 to 9 days (clinical cure and microbiological eradication in the modified intention to treat (ITT) population with bacteraemia)												
1[3]	randomised trials	serious risk of bias[4]	not applicable	no serious indirectness	serious[5]	none	23/29 (79.3%)	19/33 (57.6%)	% difference 21.7% (-1.6 to 41.7) NICE analysis: RR 1.38 (0.97 to 1.95)	219 more per 1000 (from 17 fewer to 547 more)	⊕⊕OO LOW	CRITICAL
Composite cure[1] at 5 to 9 days (clinical cure and microbiological eradication in the modified intention to treat (ITT) population resistant to levofloxacin at baseline[6])												
1[3]	randomised trials	serious risk of bias[4]	not applicable	no serious indirectness	serious[5]	none	60/100 (60%)	44/112 (39.3%)	% difference 20.7 (7.2 to 33.2) NICE analysis: RR 1.53 (1.15 to 2.02)	208 more per 1000 (from 59 more to 401 more)	⊕⊕OO LOW	CRITICAL
Adverse effects (total)												
1[3]	randomised trials	serious risk of bias[4]	not applicable	no serious indirectness	no serious imprecision	serious[7]	161/533 (30.2%)	142/535 (26.5%)	Not reported NICE analysis: RR 1.14 (0.94 to 1.38)	3 more per 1000 (from 37 fewer to 50 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: RR, Relative risk; ITT, Intention to treat; 95% CI, Confidence interval; RCT, Randomised controlled trial												

[1] Clinical cure defined as complete resolution, substantial improvement or return to pre-infection signs or symptoms of infection without the need for further antibiotics; microbiological eradication defined as $>10^4$ colony forming units per mL of the baseline uropathogen at test of cure visit urine sample

[2] Also per protocol population analysis (8.0% difference, 95% CI 2.0 to 14.0)
[3] ASPECT-cUTI (Wagenlehner et al. 2015; Armstrong et al. 2016; Huntington et al. 2016)
[4] Downgraded 1 level – selection bias present in Wagenlehner et al. 2015, as reported by authors
[5] Downgraded 1 level - at a default minimal important difference of 25% data are consistent with meaningful difference or appreciable benefit with ceftolozane-tazabactam
[6] Also composite cure sensitive to levofloxacin 3.8% difference (95% CI -26.0 to 10.3) and composite cure for ESBL +ve (62.3% versus 35.1%; 27.2% difference [95% CI 9.2 to 42.9])
[7] Downgraded 1 level - the authors report 185 of 553 (34.7%) in the ceftolozane-tazobactam group and 184 of 535 (34.4%) in the levofloxacin group had adverse events, however this does not match the 161 of 533 and 142 of 535 reported in table 3 of the authors study (still non-significant result RR 1.01, 95% CI 0.86 to 1.19)

Table 5: GRADE profile – ciprofloxacin versus ceftazidime

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ciprofloxacin	Ceftazidime	Relative (95% CI)	Absolute		
Clinical cure[1] at early follow-up at 5 to 7 days in those with percutaneous nephrostomy												
1[2]	randomised trials	very serious[3]	Not applicable	no serious indirectness	serious[4, 5]	none	45/61 (73.8%)	56/63 (88.9%)	OR 8.015 (5.732 to 11.821) NICE analysis: RR 1.20 (1.01 to 1.43)	178 more per 1000 (from 9 more to 382 more)	⊕OOO VERY LOW	CRITICAL
Clinical cure[1] at early follow-up at 5 to 7 days in those with ureteral stenting												
1[2]	randomised trials	very serious[3]	Not applicable	no serious indirectness	serious[4, 5]	none	38/58 (65.5%)	47/59 (79.7%)	OR 11.023 (5.733 to 14.428) NICE analysis: RR 1.22 (0.97 to 1.53)	175 more per 1000 (from 24 fewer to 422 more)	⊕OOO VERY LOW	CRITICAL
Microbiological cure at early follow-up at 5 to 7 days in those with percutaneous nephrostomy[6]												
1[2]	randomised trials	very serious[3]	Not applicable	no serious indirectness	serious[4, 5]	none	37/55 (67.3%)	48/56 (85.7%)	OR 9.27 (5.623 to 12.742) NICE analysis: RR 1.27 (1.03 to 1.58)	231 more per 1000 (from 26 more to 497 more)	⊕OOO VERY LOW	CRITICAL
Microbiological cure at early follow-up at 5 to 7 days in those with ureteral stenting[6]												
1[2]	randomised trials	very serious[3]	Not applicable	no serious indirectness	serious[4, 5]	none	28/49 (57.1%)	40/51 (78.4%)	OR 12.04 (6.434 to 15.731) NICE analysis: RR 1.37 (1.04 to 1.82)	290 more per 1000 (from 31 more to 643 more)	⊕OOO VERY LOW	CRITICAL
Clinical cure[1] at late follow-up at 20 to 21 days in those with percutaneous nephrostomy												
1[2]	randomised trials	very serious[3]	Not applicable	no serious indirectness	serious[4, 5]	none	51/61 (83.6%)	60/63 (95.2%)	OR 7.85 (4.608 to 10.235) NICE analysis: RR 1.14 (1.01 to 1.29)	133 more per 1000 (from 10 more to 276 more)	⊕OOO VERY LOW	CRITICAL
Clinical cure[1] at late follow-up at 20 to 21 days in those with ureteral stenting												
1[2]	randomised trials	very serious[3]	Not applicable	no serious indirectness	serious[4, 5]	none	43/58 (74.1%)	51/59 (86.4%)	OR 8.643 (5.724 to 11.229) NICE analysis: RR 1.17 (0.97 to 1.40)	147 more per 1000 (from 26 fewer to 346 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ciprofloxacin	Ceftazidime	Relative (95% CI)	Absolute		
Microbiological cure at late follow-up at 20 to 21 days following percutaneous nephrostomy												
1[2]	randomised trials	very serious[3]	Not applicable	no serious indirectness	serious[4, 5]	none	44/55 (80%)	52/56 (92.9%)	OR 7.743 (5.607 to 8.324) NICE analysis: RR 1.16 (1.0 to 1.35)	149 more per 1000 (from 0 more to 325 more)	⊕OOO VERY LOW	CRITICAL
Microbiological cure at late follow-up at 20 to 21 days in those with ureteral stenting												
1[2]	randomised trials	very serious[3]	Not applicable	no serious indirectness	serious[4, 5]	none	39/49 (79.6%)	42/51 (82.4%)	OR 7.652 (4.727 to 9.223) NICE analysis: RR 1.19 (0.95 to 1.49)	156 more per 1000 (from 41 fewer to 404 more)	⊕OOO VERY LOW	CRITICAL
Safety and tolerability (adverse effects, number of events)												
1[2]	randomised trials	very serious[3]	Not applicable	no serious indirectness	serious[4, 7]	none	41/119 (34.5%)	14/122 (11.5%)	Not reported NICE analysis: RR 3.00 (1.73 to 5.21)	230 more per 1000 (from 84 more to 483 more)	⊕OOO VERY LOW	CRITICAL
Safety and tolerability (adverse effects, number of people with adverse events)												
1[2]	randomised trials	very serious[3]	Not applicable	no serious indirectness	serious [4, 7]	none	14/119 (11.8%)	5/122 (4.1%)	Not reported NICE analysis: RR 2.87 (1.07 to 7.72)	77 more per 1000 (from 3 more to 275 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: RR, Relative risk; OR, Odds ratio; 95% CI, Confidence interval; RCT, Randomised controlled trial												

[1] Clinical cure defined as significant reduction or surcease of all symptoms and signs of disease
[2] Pasiechnikov et al. 2015
[3] Downgraded 2 levels - unclear method of randomisation, no method of blinding discussed, unclear if groups we similar at baseline
[4] Downgraded 1 level - at a default minimal important difference of 25% data suggest no meaningful difference or appreciable benefit with ceftazidime
[5] There is uncertainty over the reported OR in this analysis, personal communication with authors suggests there may be overestimation of effect in their calculation
[6] Pathogen growth of <10^3 CFU/mL from urine
[7] Downgraded 1 level – very wide 95% confidence intervals

Table 6: GRADE profile – ertapenem versus ceftriaxone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ertapenem	Ceftriaxone	Relative (95% CI)	Absolute		
Favourable microbiological response[1] at early follow-up at 5 to 9 days after therapy in the modified intention to treat population												
1[2]	randomised trials	no serious risk of bias	Not applicable	no serious indirectness	no serious imprecision	none	58/66 (87.9%)	63/71 (88.7%)	% difference 0.8% (-11.7 to 10.2)	9 fewer per 1000 (from 106 fewer	⊕⊕⊕⊕ HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ertapenem	Ceftriaxone	Relative (95% CI)	Absolute		
									NICE analysis: RR 0.99 (0.88 to 1.12)	to 106 more)		
Favourable microbiological response[1] at early follow-up at 5 to 9 days after therapy for those with acute pyelonephritis												
1[2]	randomised trials	no serious risk of bias	Not applicable	no serious indirectness	no serious imprecision	none	45/51 (88.2%)	51/57 (89.5%)	% difference 1.2% (No 95% CI not reported) NICE analysis: RR 0.99 (0.86 to 1.13)	9 fewer per 1000 (from 125 fewer to 116 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Favourable microbiological response[1] at early follow-up at 5 to 9 days after therapy for those with other complicated urinary tract infection												
1[2]	randomised trials	no serious risk of bias	Not applicable	no serious indirectness	serious[3]	none	13/15 (86.7%)	12/14 (85.7%)	% difference 1% (No 95% CI reported) NICE analysis: RR 1.01 (0.76 to 1.35)	9 more per 1000 (from 206 fewer to 300 more)	⊕⊕⊕O MODERATE	CRITICAL
Favourable microbiological response[1] at discontinuation of IV therapy for those with other complicated urinary tract infection												
1[2]	randomised trials	no serious risk of bias	Not applicable	no serious indirectness	no serious imprecision	none	14/15 (93.3%)	13/14 (92.9%)	% difference 0.5% (No 95% CI reported) NICE analysis: RR 1.01 (0.82 to 1.23)	9 more per 1000 (from 167 fewer to 214 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Favourable microbiological response[1] at discontinuation of IV therapy for those with acute pyelonephritis												
1[2]	randomised trials	no serious risk of bias	Not applicable	no serious indirectness	no serious imprecision	none	51/51 (100%)	53/57 (93%)	% difference 7% (No 95% CI reported) NICE analysis: RR 1.07 (0.99 to 1.16)	65 more per 1000 (from 9 fewer to 149 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Favourable microbiological response[1] at discontinuation of IV therapy												
1[2]	randomised trials	no serious risk of bias	Not applicable	no serious indirectness	no serious imprecision	none	65/66 (98.5%)	66/71 (93%)	% difference 5.6% (No 95% CI reported)	56 more per 1000 (from 9	⊕⊕⊕⊕ HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ertapenem**	**Ceftriaxone**	**Relative (95% CI)**	**Absolute**		
									NICE analysis: RR 1.06 (0.99 to 1.14)	fewer to 130 more)		
Favourable microbiological response[1] in those with bacteraemia												
1[2]	randomised trials	no serious risk of bias	Not applicable	no serious indirectness	very serious[4]	none	17/21 (81%)	19/23 (82.6%)	% difference 1.6% (No 95% CI reported) NICE analysis: RR 0.98 (0.74 to 1.30)	17 fewer per 1000 (from 215 fewer to 248 more)	⊕⊕OO LOW	CRITICAL
Adverse events (total) (includes diarrhoea, nausea, raised ALT/AST and local IV site reaction)												
1[2]	randomised trials	no serious risk of bias	Not applicable	no serious indirectness	very serious[3,5]	none	14/132 (10.6%)	6/135 (4.4%)	% difference 6.2% (No 95% CI reported) NICE analysis: RR 2.39 (0.95 to 6.02)	44 fewer per 1000 (from 44 fewer to 223 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: RR, Relative risk; OR, Odds ratio; 95% CI, Confidence interval; IV, Intravenous; ALT/AST, alanine aminotransferase and aspartate aminotransferase levels; RCT, Randomised controlled trial												

[1] Favourable microbiological response defined as eradication (uropathogen $\geq 10^5$ colony forming units per m/L at study entry reduced to $<10^4$ colony forming units per m/L)
[2] Park et al. 2012
[3] Downgraded 1 level - at a default minimal important difference of 25% data suggest no meaningful difference of appreciable benefit with ertapenem
[4] Downgraded 2 levels - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Downgraded 1 level - wide 95% confidence intervals

Table 7: GRADE profile – ceftazidime-avibactam versus imipenem-cilastatin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ceftazidime/ avibactam**	**Imipenem/ cilastatin**	**Relative (95% CI)**	**Absolute**		
Favourable microbiological response[1] at test of cure visit in the microbiologically evaluable population[2]												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	19/27 (70.4%)	25/35 (71.4%)	% difference 1.1% (-27.2 to 25) NICE analysis: RR 0.99 (0.71 to 1.36)	7 fewer per 1000 (from 207 fewer to 257 more)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ceftazidime/ avibactam**	**Imipenem/ cilastatin**	**Relative (95% CI)**	**Absolute**		
Favourable microbiological response[1] at the end of IV therapy in the microbiologically evaluable population												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	25/26 (96.2%)	34/34 (100%)	% difference 3.8% (No 95% CI reported) NICE analysis: RR 0.96 (0.87 to 1.06)	40 fewer per 1000 (from 130 fewer to 60 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Favourable microbiological response[1] at late follow-up in the microbiologically evaluable population[5]												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	15/26 (57.7%)	18/30 (60%)	% difference 2.3% (No 95% CI reported) NICE analysis: RR 0.96 (0.62 to 1.49)	24 fewer per 1000 (from 228 fewer to 294 more)	⊕⊕OO LOW	CRITICAL
Favourable microbiological response[1] at the test of cure visit in those with acute pyelonephritis in the microbiologically evaluable population[2]												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	13/18 (72.2%)	14/19 (73.7%)	% difference 1.5% (-35.5 to 32.6) NICE analysis: RR 0.98 (0.66 to 1.45)	15 fewer per 1000 (from 251 fewer to 332 more)	⊕⊕OO LOW	CRITICAL
Favourable microbiological response[1] at the test of cure visit in those with complicated urinary tract infection in the microbiologically evaluable population[2]												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	6/9 (66.7%)	11/16 (68.8%)	% difference 2.1% (-49 to 44.9) NICE analysis: RR 0.97 (0.55 to 1.71)	21 fewer per 1000 (from 309 fewer to 488 more)	⊕⊕OO LOW	CRITICAL
Favourable microbiological response[1] at the test of cure visit in those with *E. Coli* at baseline in the microbiologically evaluable population[2]												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	19/25 (76%)	23/33 (69.7%)	% difference 6.3% (-20.1 to 32.8) NICE analysis: RR 1.09 (0.80 to 1.49)	63 more per 1000 (from 139 fewer to 342 more)	⊕⊕OO LOW	CRITICAL
Favourable clinical response[6] at test of cure visit in the clinically evaluable population[2]												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[6]	none	24/28 (85.7%)	29/36 (80.6%)	% difference 5.2% (-16.3 to 26.6)	48 more per 1000 (from 121 fewer	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftazidime/ avibactam	Imipenem/ cilastatin	Relative (95% CI)	Absolute		
									NICE analysis: RR 1.06 (0.85 to 1.33)	to 266 more)		
Favourable microbiological response[1] at end of intravenous therapy in the intention to treat (ITT) population												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	40/46 (87%)	45/49 (91.8%)	% difference 4% (-19.4 to 9.6) NICE analysis: RR 0.95 (0.82 to 1.09)	47 fewer per 1000 (from 169 fewer to 84 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment emergent adverse events (all adverse events)												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[7]	none	46/68 (67.6%)	51/67 (76.1%)	No analysis reported NICE analysis: RR 0.89 (0.72 to 1.10)	84 fewer per 1000 (from 213 fewer to 76 more)	⊕⊕⊕O MODERATE	CRITICAL
Serious adverse events												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4, 8]	none	6/68 (8.8%)	2/67 (2.98%)	No analysis reported NICE analysis: RR 2.96 (0.62 to 14.13)	59 more per 1000 (from 11 fewer to 392 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: RR, Relative risk; 95% CI, Confidence interval; IV, Intravenous; ITT, Intention to treat; RCT, Randomised controlled trial												

[1] Favourable microbiological response defined as eradication of all uropathogens (from ≥10^5 colony forming units per m/L to <10^4 colony forming units per m/L, with no pathogen present in the blood)
[2] 5 to 9 days after last dose of study therapy
[3] Vazquez et al. 2012
[4] Downgraded 2 levels - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] 4 to 6 weeks post-therapy
[6] Favourable clinical response defined as resolution of all or most pre-therapy signs or symptoms with no further need for antibiotics
[7] Downgraded 1 level - at a default minimal important difference of 25% data suggest no meaningful difference or appreciable benefit with ceftazidime / avibactam
[8] Downgraded 1 level - very wide 95% confidence intervals

Table 8: GRADE profile – cephalothin versus ampicillin plus gentamicin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalothin	Ampicillin plus gentamicin	Relative (95% CI)	Absolute		
Duration of hospitalisation (mean duration in hours; Better indicated by lower values)												

1[1]	randomised trials	very serious[2]	not applicable	no serious indirectness	Serious[3,4]	none	N=30 (61.2 hours)	N=30 (66 hours)	-	Mean 4.8 hours lower (favours ampicillin / gentamicin, p=0.22)	⊕OOO VERY LOW	CRITICAL
Lower urinary tract symptoms (mean duration in hours; Better indicated by lower values)												
1[1]	randomised trials	very serious[2]	not applicable	no serious indirectness	Serious[3]	none	N=30 (22.5 hours)	N=30 (23.7 hours)	-	Mean 1.2 hours difference (p=NS)	⊕OOO VERY LOW	CRITICAL
Costovertebral angle tenderness (mean duration in hours; Better indicated by lower values)												
1[1]	randomised trials	very serious[2]	not applicable	no serious indirectness	Serious[3]	none	N=30 (36 hours)	N=30 (44 hours)	-	Mean 8 hours difference (p=NS)	⊕OOO VERY LOW	CRITICAL
Time to end of fever (mean duration in hours; Better indicated by lower values)												
1[1]	randomised trials	very serious[2]	not applicable	no serious indirectness	serious[3,4]	none	N=30 (19 hours)	N=30 (30 hours)	-	Mean 11 hours lower (favours ampicillin / gentamicin, p=0.01)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, Confidence interval; N, Sample size; RCT, Randomised controlled trial												

[1] Moramezi et al. 2008
[2] Downgraded 2 levels - Unclear method of randomisation, patients, health workers and study personnel not blinded, unclear if groups were similar at the start of the trial, unclear if all patients were accounted for at the end of the trial, not all clinically important outcomes were covered by the study (for example safety and adverse events were not reported)
[3] Downgraded 1 level - No 95% confidence intervals provided, insufficient data for NICE analysis (no standard deviations reported by authors)
[4] Result significant, p=0.01, but no confidence intervals are provided

Table 9: GRADE profile – levofloxacin versus ciprofloxacin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levofloxacin	Ciprofloxacin	Relative (95% CI)	Absolute		
Microbiological eradication[1] at post therapy, study days 15 to 19 (10 to 14 days post levofloxacin and 5 to 9 days post ciprofloxacin)[2]												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	253/317 (79.8%)	241/302 (79.8%)	% difference 0% (-6.3 to 6.3) NICE analysis: RR 1.00 (0.92 to 1.08)	0 fewer per 1000 (from 64 fewer to 64 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical success[4] at post therapy at post therapy, study days 15 to 19 (10 to 14 days post levofloxacin and 5 to 9 days post ciprofloxacin)[2]												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	257/317 (81.1%)	242/302 (80.1%)	% difference 0.9% (-7.2 to 5.3) NICE analysis: RR 1.01 (0.94 to 1.09)	8 more per 1000 (from 48 fewer to 72 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Microbiological eradication[1] at end of therapy, study day 11±1 (5 to 7 days post levofloxacin, 0 to 2 days post ciprofloxacin)[2]												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	253/317 (79.8%)	234/302 (77.5%)	% difference 2.3% (-8.8 to 4.1)	23 more per 1000 (from 39		CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levofloxacin	Ciprofloxacin	Relative (95% CI)	Absolute		
									NICE analysis: RR 1.03 (0.95 to 1.12)	fewer to 93 more)	⊕⊕⊕⊕ HIGH	
Clinical success[4] at end of therapy, study day 11±1 (5 to 7 days post levofloxacin, 0 to 2 days post ciprofloxacin)[2]												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	262/317 (82.6%)	237/302 (78.5%)	% difference 4.1% (-10.4 to 2.1) NICE analysis: RR 1.05 (0.97 to 1.14)	39 more per 1000 (from 24 fewer to 110 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Microbiological eradication[1] at post therapy, study days 15 to 19 (10 to 14 days post levofloxacin and 5 to 9 days post ciprofloxacin)[5]												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[7]	none	30/38 (78.9%)	16/30 (53.3%)	% difference Not reported (3.6 to 47.7) NICE analysis: RR 1.48 (1.02 to 2.15)	256 more per 1000 (from 11 more to 613 more)	⊕⊕⊕O MODERATE	CRITICAL
≥1 treatment emergent adverse event[6]												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[7]	none	192/543 (35.4%)	185/559 (33.1%)	% difference Not reported (-7.9 to 3.3) NICE analysis: RR 1.07 (0.91 to 1.26)	23 more per 1000 (from 30 fewer to 86 more)	⊕⊕⊕O MODERATE	CRITICAL
Serious adverse events												
1[3]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[8]	none	17/543 (3.13%)	15/559 (2.7%)	NICE analysis: RR 1.17 (0.59 to 2.31)	5 more per 1000 (from 11 fewer to 36 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: RR, Relative risk; 95% CI, Confidence interval; ITT, Intention to treat; RCT, Randomised controlled trial												

[1] Microbiological eradication defined as elimination or reduction of pathogens seen at study entry to $<10^4$ colony forming units per m/L
[2] In the modified intention to treat (ITT) population
[3] Peterson et al. 2008
[4] Clinical success defined as clinical cure (resolution of pre-treatment clinical signs and symptoms without additional antibacterial therapy) or clinical improvement (improvement with incomplete resolution of symptoms and no further need for antibacterial therapy)
[5] in catheterised patients
[6] Most commonly nausea, headache and diarrhoea
[7] Downgraded 1 level - at a default minimal important difference of 25% data suggest no meaningful difference or appreciable benefit/harm with levofloxacin
[8] Downgraded 2 levels - at a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm, only 1 serious adverse event was considered treatment related (allergy reaction in a levofloxacin treated individual), there were 2 deaths (one in each group) neither was treatment related.

Table 10: GRADE profile – ciprofloxacin versus co-trimoxazole

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ciprofloxacin	Co-trimoxazole	Relative (95% CI)	Absolute		
Continued bacteriologic cure[1] post therapy (visit 4 to 11 days after treatment)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	no serious imprecision	none	112/113 (99.1%)	90/101 (89.1%)	% difference 10% (0.04 to 0.16)[4] NICE analysis: RR 1.11 (1.04 to 1.19)	98 more per 1000 (from 36 more to 169 more)	⊕⊕⊕O MODERATE	CRITICAL
Continued bacteriological cure[1] post therapy (visit 22 to 48 days after treatment)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[5]	none	94/111 (84.7%)	80/108 (74.1%)	% difference 11% (0 to 0.21) NICE analysis: RR 1.14 (1.00 to 1.31)	104 more per 1000 (from 0 more to 230 more)	⊕⊕OO LOW	CRITICAL
Continued clinical cure[6] post therapy (visit 4 to 11 days after treatment)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[5]	none	109/113 (96.5%)	92/111 (82.9%)	% difference 13% (0.06 to 0.22)[7] NICE analysis: RR 1.16 (1.06 to 1.28)	133 more per 1000 (from 50 more to 232 more)	⊕⊕OO LOW	CRITICAL
Continued clinical cure[6] post therapy (visit 22 to 48 days after treatment)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[5]	none	96/106 (90.6%)	82/106 (77.4%)	% difference 14% (0.03 to 0.23)[8] NICE analysis: RR 1.17 (1.04 to 1.32)	132 more per 1000 (from 31 more to 248 more)	⊕⊕OO LOW	CRITICAL
Continued bacteriologic cure[1] (intention to treat (ITT) analysis)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[5]	none	128/153 (83.7%)	112/152 (73.7%)	% difference 10% (0.01 to 0.19) NICE analysis: RR 1.14 (1.01 to 1.28)	103 more per 1000 (from 7 more to 206 more)	⊕⊕OO LOW	CRITICAL
Continued clinical cure[6] (intention to treat (ITT) analysis)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[5]	none	137/167 (82%)	124/172 (72.1%)	% difference 10 (0.01 to 0.19)	101 more per 1000	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ciprofloxacin	Co-trimoxazole	Relative (95% CI)	Absolute		
									NICE analysis: RR 1.14 (1.01 to 1.28)	(from 7 more to 202 more)		
Adverse events (any adverse event[8])												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[5]	none	46/191 (24.1%)	62/187 (33.2%)	No analysis reported NICE analysis: RR 0.73 (0.53 to 1.00)	90 fewer per 1000 (from 156 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
Adverse events (causing discontinuation of therapy)												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[5]	none	11/191 5.7%	21/187 11.2%	NICE analysis: RR 0.51, 95% CI 0.25 to 1.03	N/A	⊕⊕OO LOW	CRITICAL
Abbreviations: RR, Relative risk; 95% CI, Confidence interval; ITT, Intention to treat; p, P Value; RCT, Randomised controlled trial												

[1] Continued bacteriologic cure defined as pathogen growth of <104 (clean catch) or < 103 (catheter specimen) colony forming units per m/L
[2] Talan et al. 2000
[3] Downgraded 1 level - unclear method of assignment of patients to treatment, unclear if groups were comparable at baseline
[4] p=0.004
[5] Downgraded 1 level - at a default minimal important difference of 25% data suggest there is no meaningful difference or appreciable benefit with ciprofloxacin
[6] Continued clinical cure defined as absence of all signs and symptoms of illness through the post-therapy follow-up visits
[7] p=0.002
[8] p=0.02
[8] Comprises adverse event leading to study discontinuation, digestive adverse events, central nervous system adverse events and rashes

Table 11: GRADE profile – short course (≤7 days) versus long course (>7 days) of antibiotics[1]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-course antibiotic (≤7 days)	Long-course antibiotic (>7 days)	Relative (95% CI)	Absolute		
Clinical failure at the end of the long treatment arm (assessed: using the same or different antibiotic comparator[2])												
5[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	37/549 (6.7%)	59/527 (11.2%)	RR 0.63 (0.33 to 1.18)	41 fewer per 1000 (from 75 fewer to 20 more)	⊕⊕OO LOW	CRITICAL
Clinical failure at end of follow-up (assessed at 22 to 63 days post therapy, and in 1 study at 6 months[2])												
7[3]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[5]	none	54/706 (7.6%)	66/692 (9.5%)	RR 0.79 (0.56 to 1.12)	20 fewer per 1000 (from 42 fewer to 11 more)	⊕⊕OO LOW	CRITICAL
Clinical failure in people with bacteraemia (assessed at end of follow-up in sub-group analysis)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-course antibiotic (≤7 days)	Long-course antibiotic (>7 days)	Relative (95% CI)	Absolute		
4[3]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[7]	none	2/35 (5.7%)	6/51 (11.8%)	RR 0.54 (0.15 to 1.92)	54 fewer per 1000 (from 100 fewer to 108 more)	⊕OOO VERY LOW	CRITICAL
Microbiological failure at end of follow-up (assessed in the microbiologically evaluable population)												
8[3]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[5]	none	130/715 (18.2%)	116/687 (16.9%)	RR 1.16 (0.83 to 1.62)	27 more per 1000 (from 29 fewer to 105 more)	⊕⊕OO LOW	CRITICAL
Microbiological failure at end of follow-up (assessed in sub-group analysis of studies with more than 20% of patients with urogenital abnormalities[10])												
1[3]	randomised trials	serious[12]	serious[13]	no serious indirectness	serious[5]	none	N≈100		RR 1.78 (1.02 to 3.10)	Not estimable	⊕OOO VERY LOW	CRITICAL
Adverse effects												
7[3]	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	serious[5]	none	N=2127		RR 0.93 (0.73 to 1.18)	Not estimable	⊕⊕OO LOW	CRITICAL
Adverse events requiring discontinuation of therapy												
7[3]	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	serious[5]	none	N=2,127		RR 0.78 (0.52 to 1.18)	Not estimable	⊕⊕OO LOW	CRITICAL
Mortality												
2[3]	randomised trials	no serious risk of bias	serious[13]	no serious indirectness	serious[13]	none	In a single study there was 1 death in each arm (no further details reported). 1 other study reported no deaths.			Not estimable	⊕⊕OO LOW	CRITICAL
Microbial resistance												
5[3]	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	serious[13]	none	3 of 5 studies reported no development of resistance. 2 studies reported equal numbers (1 or 2 cases) in each arm.				⊕⊕OO LOW	CRITICAL
Length of stay												
1[3]	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	serious[13]	none	A single study reported length of hospitalisation which was shorter in the short treatment arm (no further details given)				⊕⊕OO LOW	CRITICAL
Abbreviations: N = sample size; : RR, Relative risk; 95% CI, Confidence interval; RCT, Randomised controlled trial												

[1] Aged >16 years
[2] in the as treated population (per protocol)
[3] Eliakim-Raz et al. 2013
[4] Downgraded 1 level - 2 of the five studies accounting for 46% weight in the meta-analysis were assessed by the authors as being at increased risk of bias
[5] Downgraded 1 level - at a default minimal important difference of 25% data suggest there is no meaningful difference or appreciable benefit with 7 days or fewer of antibiotics
[6] Downgraded 1 level - 4 of the seven studies accounting for 57.4% weight in the meta-analysis were assessed by the authors as being at increased risk of bias
[7] Downgraded 1 level - 2 of the 4 studies accounting for 33.2% weight in the meta-analysis were assessed by the authors as being at increased risk of bias
[8] Downgraded 2 levels – at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[9] Downgraded 1 level - 5 of the 8 studies accounting for 71.7% weight in the meta-analysis were assessed by the authors as being at increased risk of bias

[10] Number of randomised trials not reported (n=287 of whom about 100 had urogenital abnormality)
[12] Downgraded 1 level - 2 of the 3 studies in the meta-analysis were assessed by the authors as being at increased risk of bias
[13] Downgraded 1 level - not assessable (insufficient data reported)
[14] Downgraded 1 level - unable to ascertain which 7 RCTs were included in this analysis (but over half the 8 included studies were at increased risk of bias)
[14] Downgraded 1 level - the studies reporting development of resistance were assessed as at higher risk of bias than those that reported the same outcome but found no resistance
[15] Downgraded 1 level - the single study was assessed as at higher risk of bias by the authors

Table 12: GRADE profile – 7 to 14 days versus 14 to 42 days of antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	7 to 14 days antibiotic	14 to 42 days antibiotic	Relative (95% CI)	Absolute		
Clinical success (assessed with: resolution of signs and symptoms at test-of-cure visit)												
4[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	91/110 (82.7%)	72/89 (80.9%)	OR 1.27 (0.59 to 2.7) NICE analysis: RR 1.04 (0.91 to 1.19)	32 more per 1000 (from 73 fewer to 154 more)	⊕⊕⊕O MODERATE	CRITICAL
Bacteriologic efficacy (assessed with: sterile urine culture or +ve culture <10^3 CFU/mL)												
4[1]	randomised trials	serious[2]	serious[4]	no serious indirectness	very serious[3]	none	79/110 (71.8%)	67/89 (75.3%)	OR 0.80 (0.13 to 4.95) NICE analysis: RR 0.93 (0.63 to 1.37)	53 fewer per 1000 (from 279 fewer to 279 more)	⊕OOO VERY LOW	CRITICAL
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	9/32 (28.1%)	20/29 (68.9%)	OR 0.18 (0.06 to 0.53) NICE analysis: RR 0.41 (0.22 to 0.75)	407 fewer per 1000 (from 538 fewer to 172 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Relapse (assessed with: appearance of the original uropathogen between the test-of-cure and follow-up visits)												
4[1]	randomised trials	serious[2]	serious[4]	no serious indirectness	very serious[3]	none	21/110 (19.1%)	15/89 (16.9%)	OR 0.65 (0.08 to 5.39) NICE analysis: RR 0.66 (0.12 to 3.62)	57 fewer per 1000 (from 148 fewer to 442 more)	⊕OOO VERY LOW	CRITICAL
Recurrence (assessed with: the appearance of another bacteriologic strain in a urine culture between the test of cure visit and follow up visit)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	7 to 14 days antibiotic	14 to 42 days antibiotic	Relative (95% CI)	Absolute		
4[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	20/110 (18.2%)	12/89 (13.5%)	OR 1.39 (0.63 to 3.06) NICE analysis: RR 1.32 (0.68 to 2.55)	43 more per 1000 (from 43 fewer to 209 more)	⊕OOO VERY LOW	CRITICAL
Adverse events												
4[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	19/131 (14.5%)	26/127 (20.5%)	OR 0.64 (0.33 to 1.25) NICE analysis: RR 0.71 (0.42 to 1.20)	59 fewer per 1000 (from 119 fewer to 41 more)	⊕⊕⊕O MODERATE	CRITICAL
Withdrawals due to adverse events												
4[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/131 (7.6%)	13/127 (10.2%)	OR 0.65 (0.28 to 1.55) NICE analysis: RR 0.69 (0.33 to 1.47)	32 fewer per 1000 (from 69 fewer to 48 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CFU/mL, Colony forming units per mL; RR, Relative risk; OR, Odds ratio; 95% CI, Confidence interval; RCT, Randomised controlled trial												

[1] Kyriakidou et al. 2008
[2] Downgraded 1 level - Only 1 study in the meta-analysis was assessed as being at low risk of bias
[3] Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[4] Downgraded 1 level – due to heterogeneity (I^2>50%)
[5] Downgraded 1 level - at a default minimal important difference of 25% data suggest there is no meaningful difference or appreciable benefit with 7 to 14 days of antibiotic therapy

Table 13: GRADE profile – 5 days levofloxacin (750 mg) versus 7 to 14 days levofloxacin (500 mg)

Quality assessment							No of patients		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levofloxacin 750 mg per day for 5 days (IV)	Levofloxacin 500 mg per day for 7 to 14 days (oral or IV)	R (9
Clinical effectiveness rate at end of therapy (assessed with: complete remission of signs and symptoms or reduction of same in an ITT population)									

Quality assessment							No of patients		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levofloxacin 750 mg per day for 5 days (IV)	Levofloxacin 500 mg per day for 7 to 14 days (oral or IV)	R (9
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	142/158 (89.9%)	142/159 (89.3%)	% d 0.5 t ana 0.9
Clinical effectiveness rate at end of therapy (assessed with: complete remission of signs and symptoms or reduction of same[3])									
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	69/72 (95.8%)	66/69 (95.7%)	Not ana 1.0
Clinical effectiveness rate at end of therapy (assessed with: complete remission of signs and symptoms or reduction of same[4])									
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	73/86 (84.9%)	76/90 (84.4%)	Not ana 1.0
Clinical success rate for acute pyelonephritis (APN) versus complicated urinary tract infection (cUTI) at end of therapy (assessed with: people who had complete success and remission[3, 4])									
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	135/141 APN both doses (750 and 500 mg)	149/176 cUTI both doses (750 and 500 mg)	p< bo com ana 1.1
Microbiological eradication rate (assessed with: In the ITT population)									
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	60/67 (89.6%)	63/73 (86.3%)	p ana 0.9
Time to clinical success (measured with: days; Better indicated by lower values)									
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[5]	none	N=158 (Median 3 days)	N=159 (Median 4 days)	n di (p
Total adverse events									

Quality assessment							No of patients		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levofloxacin 750 mg per day for 5 days (IV)	Levofloxacin 500 mg per day for 7 to 14 days (oral or IV)	R (9
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[6]	none	36/164 (22%)	38/165 (23%)	Not ana 0.9
Severe adverse events									
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[6]	none	1/164 (0.61%)	2/165 (1.21%)	p ana 0.5
Adverse events related to treatment									
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[6]	none	31/164 (18.9%)	26/165 (15.76%)	p ana 1.2
Abbreviations: N, sample size; RR, Relative risk; 95% CI, Confidence interval; ITT, Intention to treat; RCT, Randomised controlled trial									

[1] Ren Hong et al. 2017
[2] Downgraded 1 level - open label study, with unclear method of randomisation
[3] In the ITT population with acute pyelonephritis
[4] In the ITT population with complicated urinary tract infection
[5] Downgraded 1 level – not assessable p>0.05 suggests no significant difference between intervention and comparator
[6] Downgraded 2 levels – at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 14: GRADE profile – sequential intravenous then oral antibiotics versus injected antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sequential IV then oral antibiotics[1]	Injected antibiotics[2]	Relative (95% CI)	Absolute		
Fever after 48 hours												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	very serious[5]	none	0/10 (0%)	2/10 (20%)	RR 5.00 (0.27 to 92.62)	800 more per 1000 (from 146 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Bacterial eradication under therapy												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sequential IV then oral antibiotics[1]	Injected antibiotics[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	serious[6]	none	7/9 (77.8%)	10/10 (100%)	RR 0.79 (0.54 to 1.15)	210 fewer per 1000 (from 460 fewer to 150 more)	⊕⊕OO LOW	CRITICAL
Clinical cure at end of therapy												
2[3]	randomised trials[7]	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	63/66 (95.5%)	67/71 (94.4%)	RR 1.01 (0.94 to 1.1)	9 more per 1000 (from 57 fewer to 94 more)	⊕⊕⊕O MODERATE	CRITICAL
Bacterial cure at end of therapy												
2[3]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[6]	none	36/37 (97.3%)	36/39 (92.3%)	RR 1.05 (0.95 to 1.17)	102 more per 1000 (from 92 fewer to 332 more)	⊕⊕OO LOW	CRITICAL
Composite cure at end of therapy (assessed with: bacteriological and clinical cure)												
4[3]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	133/142 (93.7%)	141/152 (92.8%)	RR 0.99 (0.94 to 1.04)	9 fewer per 1000 (from 56 fewer to 37 more)	⊕⊕⊕O MODERATE	CRITICAL
Reinfection at end of therapy												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	very serious[5]	none	2/36 (5.6%)	2/36 (5.6%)	RR 1.00 (0.15 to 6.72)	0 fewer per 1000 (from 47 fewer to 318 more)	⊕OOO VERY LOW	CRITICAL
Composite cure after an interval (assessed with: bacteriological and clinical cure[10])												
3[3]	randomised trials	serious[11]	serious[12]	no serious indirectness	no serious imprecision	none	94/106 (88.7%)	102/113 (90.3%)	RR 0.99 (0.89 to 1.11)	9 fewer per 1000 (from 99 fewer to 99 more)	⊕⊕OO LOW	CRITICAL
Relapse after an interval												
3[3]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/98 (1%)	3/105 (2.9%)	RR 2.79 (0.3 to 25.67)	51 more per 1000 (from 20 fewer to 705 more)	⊕OOO VERY LOW	CRITICAL
Renal scarring after 6 months												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	very serious[5]	none	12/18 (66.7%)	11/18 (61.1%)	RR 0.92 (0.56 to 1.5)	49 fewer per 1000 (from 269 fewer to 306 more)	⊕OOO VERY LOW	CRITICAL
Adverse events												
4[3]	randomised trials	serious[13]	no serious inconsistency	no serious indirectness	very serious[5]	none	13/142 (9.2%)	14/150 (9.3%)	RR 0.85 (0.19 to 3.83)	14 fewer per 1000 (from 76 fewer to 264 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: RR, Relative risk; 95% CI, Confidence interval; IV, Intravenous; IM, Intramuscular; RCT, Randomised controlled trial												

[1] Initial IV therapy (cefotaxime, amoxicillin/clavulanic acid, ceftriaxone, ceftazidime, ciprofloxacin, netilmicin, amikacin and gentamicin) followed by oral antibiotics (ciprofloxacin, amoxicillin/clavulanic acid, cefixime or ceftibuten)

[2] IV or IM antibiotics

[3] Pohl A. 2010
[4] Downgraded 1 level - 1 study at high risk of bias in the analysis
[5] Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Downgraded 1 level - at a default minimal important difference of 25% data suggest no meaningful difference or appreciable benefit or harm with switch therapy
[7] Duration of therapy varied by study from 4 to 14 days
[8] Downgraded 1 level - no studies were assessed by Cochrane reviewers as being at low risk of bias, 2 studies both at higher risk of bias were included in the meta-analysis
[9] Downgraded 1 level - no studies were assessed by Cochrane reviewers as being at low risk of bias, 4 studies at higher risk of bias were included in the meta-analysis
[10] in subgroup analysis of studies for children RR 1.03 (95% CI 0.96 to 1.10) 2 studies, n=138, I^2=6% follow-up at between 10 and 20 days and 14 days in the 2 studies; and 1 study, follow-up at 10 to 84 days, in adults RR 0.92 (95% CI 0.73 to 1.16) n=81, I^2=NA
[11] Downgraded 1 level - no studies were assessed by Cochrane reviewers as being at low risk of bias, 3 studies at higher risk of bias were included in the meta-analysis
[12] Downgraded 1 level - due to heterogeneity (I^2=39%)
[13] Downgraded 1 level - no studies were assessed by Cochrane reviewers as being at low risk of bias, 4 studies at higher risk of bias were included in the meta-analysis

Table 15: GRADE profile – sequential intravenous then oral antibiotics versus oral antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sequential IV then oral antibiotics	Oral antibiotics	Relative (95% CI)	Absolute		
Clinical and bacteriological cure under therapy												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	292/294 (99.3%)	300/305 (98.4%)	RR 1.00 (0.98 to 1.02)	0 fewer per 1000 (from 20 fewer to 20 more)	⊕⊕⊕O MODERATE	CRITICAL
Rate of reinfection at end of therapy												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	2/29 (6.9%)	2/25 (8%)	RR 1.16 (0.18 to 7.74)	13 more per 1000 (from 66 fewer to 539 more)	⊕OOO VERY LOW	CRITICAL
Relapse at end of therapy												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	2/29 (6.9%)	0/25 (0%)	RR 0.23 (0.01 to 4.59)	-	⊕OOO VERY LOW	CRITICAL
Renal scarring after 6 months (assessed with DMSA scan)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	44/212 (20.8%)	36/212 (17%)	RR 0.87 (0.35 to 2.16)	22 fewer per 1000 (from 110 fewer to 197 more)	⊕OOO VERY LOW	CRITICAL
Mean time to cessation of fever (Better indicated by lower values)												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	424	410	-	MD 0.40 higher (2.94 lower to 3.74 higher)	⊕⊕OO LOW	CRITICAL
Adverse effects												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/259 (0.39%)	1/247 (0.4%)	RR 0.96 (0.06 to 15.02)	0 fewer per 1000 (from 4 fewer to 57 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: RR, Relative risk; 95% CI, Confidence interval; RCT, Randomised controlled trial												

[1] Pohl A. 2007
[2] Downgraded 1 level - no study was assessed by the Cochrane reviewer as being at low risk of bias
[3] Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[4] Downgraded 1 levels - at a default minimal important difference of 0.5 SD of comparator arm data suggest no meaningful difference or appreciable benefit with oral therapy

Table 16: GRADE profile – oral antibiotics versus injected antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral antibiotics	Injected antibiotics	Relative (95% CI)	Absolute		
Bacteriological cure at end of therapy (oral norfloxacin versus aztreonam)												
1[1]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[4]	none	13/18 (72.2%)	20/20 (100%)	RR 1.37 (1.02 to 1.84)[4]	370 more per 1000 (from 20 more to 840 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: RR, Relative risk; 95% CI, Confidence interval; RCT, Randomised controlled trial												

[1] Pohl A. 2007
[2] Downgraded 1 level - no study assessed by the Cochrane reviewer was found to be at low risk of bias
[3] Downgraded 1 level - at a default minimal important difference of 25% data suggest no meaningful difference or appreciable benefit or harm with parenteral therapy
[4] the effect became more pronounced after an interval (RR 1.95, 95% CI 1.24 to 3.08; low quality evidence)

Table 17: GRADE profile – sequential intravenous then oral antibiotics versus single injected dose then oral antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sequential IV then oral antibiotics	Single injected dose then oral antibiotics	Relative (95% CI)	Absolute		
Clinical cure under therapy (not defined)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103/114 (90.4%)	107/111 (96.4%)	RR 0.93 (0.86 to 1.02)[3]	67 fewer per 1000 (from 135 fewer to 19 more)	⊕⊕⊕O MODERATE	CRITICAL
Bacterial eradication at end of therapy												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	41/53 (77.4%)	46/57 (80.7%)	RR 0.96 (0.79 to 1.16)	32 fewer per 1000 (from 169 fewer to 129 more)	⊕⊕⊕O MODERATE	CRITICAL
Mean time to cessation of fever (better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	N=51 (mean 1.6 days [SD 0.8])	N=54 (mean 1.6 days [SD 0.7])	-	MD 0.10 higher (0.19 lower to 0.39 higher)	⊕⊕OO LOW	CRITICAL
Duration of symptoms (better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sequential IV then oral antibiotics	Single injected dose then oral antibiotics	Relative (95% CI)	Absolute		
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	N=51 (mean 2.3 days [SD 1.1])	N=54 (mean 2 days [SD 1.3])	-	MD 0.30 higher (0.16 lower to 0.76 higher)	⊕⊕OO LOW	CRITICAL
Adverse event rate												
2[1]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/114 (0.88%)	4/111 (3.6%)	RR 4.00 (0.46 to 34.75)	108 more per 1000 (from 19 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: RR, Relative risk; 95% CI, Confidence interval; MD, Mean difference; RCT, Randomised controlled trial												

[1] Pohl A. 2007
[2] Downgraded 1 level - no studies were assessed by the Cochrane review as being at low risk of bias
[3] also bacterial cure under therapy RR 1.00 (95% CI 0.96 to 1.04; moderate quality evidence) 1 study, n=105, I^2=NA
[4] Downgraded 1 level – at a default minimal important difference of 0.5 standard deviation of comparator data suggest there is no meaningful difference or appreciable benefit with sequential intravenous then oral antibiotics
[5] Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 18: GRADE profile – single injected dose then oral antibiotics versus oral antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single injected dose then oral antibiotics	Oral antibiotics	Relative (95% CI)	Absolute		
Clinical or bacteriological cure under therapy (single shot of ceftriaxone IM 50 mg/kg once initially followed by oral trimethoprim 10 mg/kg/day for 10 days compared with oral trimethoprim 10 mg/kg/day for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	30/34 (88.2%)	30/35 (85.7%)	RR 0.97 (0.81 to 1.17)	26 fewer per 1000 (from 163 fewer to 146 more)	⊕⊕⊕O MODERATE	CRITICAL
Bacterial cure under therapy (single shot of ceftriaxone IM 50 mg/kg once initially followed by oral trimethoprim 10 mg/kg/day for 10 days compared with oral trimethoprim 10 mg/kg/day for 10 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	31/34 (91.2%)	31/35 (88.6%)	RR 0.97 (0.83 to 1.14)	27 fewer per 1000 (from 151 fewer to 124 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	4/34 (11.8%)	3/35 (8.6%)	RR 1.37 (0.33 to 5.68)	32 more per 1000 (from 57 fewer to 401 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single injected dose then oral antibiotics	Oral antibiotics	Relative (95% CI)	Absolute		
Abbreviations: RR, Relative risk; 95% CI, Confidence interval; RCT, Randomised controlled trial												

[1] Pohl A. 2007
[2] Downgraded 1 level - no study reviewed by the Cochrane assessor was assessed as at low risk of bias
[3] Downgraded 2 levels - at a default minimal important difference of 25% data suggest there is no meaningful difference or appreciable benefit or appreciable harm

H.2 Antimicrobials for acute pyelonephritis in children

Table 19: GRADE profile – third generation cephalosporins versus other antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Third generation cephalosporin	Other antibiotic	Relative (95% CI)	Absolute		
Persistent bacteriuria after 48 hours of therapy												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	24/290 (8.3%)[4]	5/149 (3.4%)[5]	RR 2.41 (0.98 to 5.93)	47 more per 1000 (from 1 fewer to 165 more)	⊕⊕OO LOW	CRITICAL
Recurrent UTI after end of therapy												
4[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	none	8/327 (2.4%)[4]	3/164 (1.8%)[5]	RR 1.23 (0.32 to 4.74)	4 more per 1000 (from 12 fewer to 68 more)	⊕OOO VERY LOW	CRITICAL
Persistent clinical symptoms after end of treatment												
3[1]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/317 (2.8%)[4]	16/154 (10.4%)[5]	RR 0.28 (0.13 to 0.62)	75 fewer per 1000 (from 39 fewer to 90 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Number with fever for longer than 48 hours												
1[1]	randomised trials	serious[8]	not applicable	no serious indirectness	very serious[6]	none	2/10 (20%)[4]	0/10 (0%)[5]	RR 5.00 (0.27 to 92.62)	-	⊕OOO VERY LOW	CRITICAL
Gastrointestinal adverse events												
4[1]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[6]	none	12/397 (3%)[4]	7/194 (3.6%)[5]	RR 0.93 (0.34 to 2.58)	3 fewer per 1000 (from 24 fewer to 57 more)	⊕OOO VERY LOW	CRITICAL
Discontinuation of treatment												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Third generation cephalosporin	Other antibiotic	Relative (95% CI)	Absolute		
1[1]	randomised trials	serious[8]	not applicable	no serious indirectness	very serious[6]	none	4/309 (1.29%)	4/152 (2.63%)	RR 0.49, 95% CI 0.12 to 1.94	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: RR, Relative risk; 95% CI, Confidence interval; RCT, Randomised controlled trial												

[1] Strohmeier Y et al. 2014
[2] Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as having low risk of bias, 1 RCT which represented 90.4% weight in the meta-analysis was at high risk of bias
[3] Downgraded 1 level - at a default minimal important difference of 25% data are consistent with no meaningful difference or appreciable benefit with cephalosporins
[4] Third generation cephalosporins (IV cefotaxime, oral cefetamet, oral ceftibuten)
[5] Other antibiotics co-amoxiclav or co-trimoxazole
[6] Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[7] Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as having low risk of bias, 1 RCT which represented 93.6% weight in the meta-analysis was at high risk of bias
[8] Downgraded 1 level - this single RCT was at moderate risk of bias as assessed by Cochrane reviewers
[9] Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as having low risk of bias, 1 RCT which represented 60.5% weight in the meta-analysis was at high risk of bias

Table 20: GRADE profile – fourth generation cephalosporins versus third generation cephalosporins

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4th generation cephalosporin (cefepime)	3rd generation cephalosporin (ceftazidime)	Relative (95% CI)	Absolute		
Persistence or recurrence of initial pathogen at 5 to 9 days after treatment												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	5/96 (5.2%)	2/91 (2.2%)	RR 2.37 (0.47 to 11.91)	30 more per 1000 (from 12 fewer to 240 more)	⊕OOO VERY LOW	CRITICAL
Persistence or recurrence at end of IV antibiotics												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	1/111 (0.9%)	0/113 (0%)	RR 3.05 (0.13 to 74.16)	-	⊕OOO VERY LOW	CRITICAL
Persistence or recurrence at end of IV and oral antibiotics												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	0/96 (0%)	4/102 (3.9%)	RR 0.12 (0.01 to 2.16)	35 fewer per 1000 (from 39 fewer to 45 more)	⊕OOO VERY LOW	CRITICAL
Persistence or recurrence at 4 to 6 weeks after treatment												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	1/91 (1.1%)	8/97 (8.2%)	RR 0.13 (0.02 to 1.04)	72 fewer per 1000 (from 81 fewer to 3 more)	⊕OOO VERY LOW	CRITICAL
Infection with new pathogen at 4 to 6 weeks												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4th generation cephalosporin (cefepime)	3rd generation cephalosporin (ceftazidime)	Relative (95% CI)	Absolute		
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	8/115 (7%)	7/120 (5.8%)	RR 1.19 (0.45 to 3.18)	11 more per 1000 (from 32 fewer to 127 more)	⊕OOO VERY LOW	CRITICAL
Unsatisfactory clinical response at 5 to 9 days after treatment												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	2/99 (2%)	0/100 (0%)	RR 5.05 (0.25 to 103.87)	-	⊕OOO VERY LOW	CRITICAL
Adverse effects (assessed with: Total number of adverse effects[5])												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	41/149 (27.5%)	37/150 (24.7%)	RR 1.12 (0.76 to 1.63)	30 more per 1000 (from 59 fewer to 155 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: RR, Relative risk; 95% CI, Confidence interval; RCT, Randomised controlled trial												

[1] Strohmeier Y et al. 2014
[2] Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as low risk of bias
[3] Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable harm or appreciable benefit
[5] Also non-significant for drug related adverse events, gastrointestinal adverse events, cutaneous adverse events and discontinuation due to adverse events

Table 21: GRADE profile – third generation cephalosporin versus another third generation cephalosporin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	Cefotaxime	Relative (95% CI)	Absolute		
Persistent bacteriuria at 48 hours												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	0/50 (0%)	0/50 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Bacteriuria 10 days after end of treatment (assessed in all patients[4])												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[5]	none	8/42 (19%)	9/41 (22%)	RR 0.87 (0.37 to 2.03)	29 fewer per 1000 (from 138 fewer to 226 more)	⊕OOO VERY LOW	CRITICAL
Urinary tract infection at 1 month after therapy (assessed in all patients[6])												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[5]	none	8/42 (19%)	11/39 (28.2%)	RR 0.68 (0.3 to 1.5)	90 fewer per 1000 (from 197 fewer to 141 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects (assessed in all adverse events[7])												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	Cefotaxime	Relative (95% CI)	Absolute		
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[5]	none	2/50 (4%)	3/50 (6%)	RR 0.67 (0.12 to 3.82)	20 fewer per 1000 (from 53 fewer to 169 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: RR, Relative risk; 95% CI, Confidence interval; RCT, Randomised controlled trial												

[1] Strohmeier Y et al. 2014
[2] Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as having low risk of bias
[3] Downgraded 2 levels - not estimable
[4] Also non-significant results for normal renal tract imaging and abnormal renal tract imaging (post hoc analyses)
[5] Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Also non-significant results for normal renal tract imaging and abnormal renal tract imaging
[7] Also non-significant results for skin eruption adverse effects and gastrointestinal adverse effects

Table 22: GRADE profile – aminoglycoside versus another aminoglycoside

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isepamicin	Amikacin	Relative (95% CI)	Absolute		
Persistent bacteriuria at 7 days after completing therapy												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	0/10 (0%)	0/6 (0%)	Not estimable		⊕OOO VERY LOW	CRITICAL
Persistent bacteriuria after 2 to 3 days of therapy												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	0/10 (0%)	0/6 (0%)	Not estimable		⊕OOO VERY LOW	CRITICAL
Persistent bacteriuria at 30 days after completing therapy												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	0/10 (0%)	0/6 (0%)	Not estimable		⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, Confidence interval; RCT, Randomised controlled trial												

[1] Strohmeier Y et al. 2014
[2] Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as having low risk of bias
[3] Downgraded 1 level - not assessable

Table 23: GRADE profile – Daily versus 8 hourly dosing of aminoglycosides

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily dosing of aminoglycoside	8 hourly dosing of aminoglycoside	Relative (95% CI)	Absolute		
Persistent bacteriuria after 1 to 3 days of treatment												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/218 (0.92%)	2/217 (0.92%)	RR 1.05 (0.15 to 7.27)	0 more per 1000 (from 8 fewer to 58 more)	⊕OOO VERY LOW	CRITICAL
Persistent symptoms at end of 3 days of IV therapy												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	4/90 (4.4%)	2/89 (2.2%)	RR 1.98 (0.37 to 10.53)	22 more per 1000 (from 14 fewer to 214 more)	⊕OOO VERY LOW	CRITICAL
Persistent bacteriuria at 1 week after treatment												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	1/74 (1.4%)	0/70 (0%)	RR 2.84 (0.12 to 68.57)	Not estimable	⊕OOO VERY LOW	CRITICAL
Reinfection at 1 month after therapy												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	5/74 (6.8%)	4/70 (5.7%)	RR 1.18 (0.33 to 4.23)	10 more per 1000 (from 38 fewer to 185 more)	⊕OOO VERY LOW	CRITICAL
Hearing impairment following treatment												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/138 (2.2%)	0/133 (0%)	RR 2.83 (0.33 to 24.56)	Not estimable	⊕OOO VERY LOW	CRITICAL
Increase in serum creatinine during treatment												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/217 (1.8%)	5/202 (2.5%)	RR 0.75 (0.2 to 2.82)	6 fewer per 1000 (from 20 fewer to 45 more)	⊕OOO VERY LOW	CRITICAL
Time to resolution of fever (measured with: mean (hours); better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	N=84	N=88	-	MD 2.40 higher (7.9 lower to 12.7 higher)	⊕⊕⊕O MODERATE	CRITICAL
Kidney parenchymal damage at 3 months												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	18/75 (24%)	23/71 (32.4%)	RR 0.74 (0.44 to 1.25)	84 fewer per 1000 (from 181 fewer to 81 more)	⊕OOO VERY LOW	CRITICAL
Time to resolution of fever (measured with: median (hours); better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	N=not reported 27 hours (IQR 15 to 48)	N=not reported 33 hours (IQR 12 to 48)	Not reported[4]	Not estimable	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Daily dosing of aminoglycoside	8 hourly dosing of aminoglycoside	Relative (95% CI)	Absolute		
Abbreviations: RR, Relative risk; IV, Intravenous; MD, Mean difference; 95% CI, Confidence interval; RCT, Randomised controlled trial												

[1] Strohmeier Y et al. 2014
[2] Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as having low risk of bias
[3] Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable harm or appreciable benefit
[4] Not assessable

Table 24: GRADE profile – 10 days versus 42 days of oral antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	10 days of oral sulphafurazole	42 days of oral sulphafurazole	Relative (95% CI)	Absolute		
Recurrent UTI within 1 month after therapy												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	17/73 (23.3%)	1/76 (1.3%)	RR 17.70 (2.42 to 129.61)	220 more per 1000 (from 19 more to 1000 more)	⊕⊕⊕O MODERATE	CRITICAL
Recurrence of UTI at 1 to 12 months after completing therapy												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[4]	none	10/73 (13.7%)	12/76 (15.8%)	RR 0.87 (0.4 to 1.88)	21 fewer per 1000 (from 95 fewer to 139 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: UTI, Urinary tract infection; 95% CI, Confidence interval; RR, Relative risk; RCT, Randomised controlled trial												

[1] Strohmeier Y et al. 2014
[2] Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as low risk of bias
[3] Downgraded 1 level - very wide confidence intervals
[4] Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable harm or appreciable benefit

Table 25: GRADE profile – single injected dose versus 7 to 10 days of oral antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single injected dose[1]	7 to 10 days of oral antibiotics	Relative (95% CI)	Absolute		
Persistent bacteriuria at 1 to 2 days after treatment												
2[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	3/18 (16.7%)	1/17 (5.9%)	RR 1.73 (0.18 to 16.3)	43 more per 1000 (from 48 fewer to 900 more)	⊕OOO VERY LOW	CRITICAL
UTI relapse or reinfection within 6 weeks												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single injected dose[1]	7 to 10 days of oral antibiotics	Relative (95% CI)	Absolute		
2[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/18 (5.6%)	3/17 (17.6%)	RR 0.24 (0.03 to 1.97)	134 fewer per 1000 (from 171 fewer to 171 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: UTI, Urinary tract infection; 95% CI, Confidence interval; RR, Relative risk; RCT, Randomised controlled trial												

[1] 2 studies, both IV, gentamicin in 1 study and cefotaxime in the second
[2] Strohmeier Y et al. 2014
[3] Downgraded 1 level - no RCTs were assessed by Cochrane as having low risk of bias
[4] Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable harm or appreciable benefit

Table 26: GRADE profile – 3 weeks versus 2 weeks of antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 weeks of antibiotics	2 weeks of antibiotics	Relative (95% CI)	Absolute		
Persistence / recurrence of bacteriuria (assessed in children with acute lobar nephronia[1])												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[4]	none	0/39 (0%)	7/41 (17.1%)	RR 0.07 (0 to 1.19)	159 fewer per 1000 (from 171 fewer to 32 more)	⊕OOO VERY LOW	CRITICAL
Recurrence of clinical UTI (assessed in children with acute lobar nephronia[1])												
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[4]	none	0/39 (0%)	2/41 (4.9%)	RR 0.21 (0.01 to 4.24)	39 fewer per 1000 (from 48 fewer to 158 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: UTI, Urinary tract infection; 95% CI, Confidence interval; RR, Relative risk; RCT, Randomised controlled trial												

[1] Antibiotics according to sensitivities
[2] Strohmeier Y et al. 2014
[3] Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as having low risk of bias
[4] Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable harm or appreciable benefit

Table 27: GRADE profile – oral antibiotics versus intravenous then oral antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral antibiotic	IV antibiotic followed by oral antibiotic (for 11 days)	Relative (95% CI)	Absolute		
Time to resolution of fever (hours) (better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral antibiotic	IV antibiotic followed by oral antibiotic (for 11 days)	Relative (95% CI)	Absolute		
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	N=397	N=411	-	MD 2.05 higher (0.84 lower to 4.94 higher)	⊕⊕⊕O MODERATE	CRITICAL
Fever on day 3												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	7/80 (8.8%)	8/72 (11.1%)	RR 0.79 (0.3 to 2.06)	23 fewer per 1000 (from 78 fewer to 118 more)	⊕OOO VERY LOW	CRITICAL
Persistent UTI at 72 hours												
2[1]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/266 (0.38%)	1/276 (0.36%)	RR 1.10 (0.07 to 17.41)	0 more per 1000 (from 3 fewer to 59 more)	⊕OOO VERY LOW	CRITICAL
Recurrent symptomatic UTI within 6 months												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	7/140 (5%)	11/147 (7.5%)	RR 0.67 (0.27 to 1.67)	25 fewer per 1000 (from 55 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL
Persistent kidney damage at 6 to 12 months (assessed with: 99m Tc-DMSA renal scan[6])												
4[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[7]	none	88/470 (18.7%)	106/473 (22.4%)	RR 0.82 (0.59 to 1.12)	40 fewer per 1000 (from 92 fewer to 27 more)	⊕⊕OO LOW	CRITICAL
Kidney damage at 6 months (assessed in post hoc subgroup analysis of children with persistent damage with VUR grades 3 to 5[8])												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[9]	none	8/24 (33.3%)	1/22 (4.5%)	RR 7.33 (1 to 54.01)	288 more per 1000 (from 0 more to 1000 more)	⊕⊕OO LOW	CRITICAL
Inflammatory markers at 72 hours (measured with: white cell count (10^9/L)[10]; better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	N=230	N=243	-	MD 0.30 higher (0.3 lower to 0.9 higher)	⊕⊕⊕O MODERATE	CRITICAL
Adverse effects												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	not applicable	none	3 RCTs reported the outcome of adverse events; 1 RCT had no adverse events during the study. 1 RCT found that 2 children in the oral antibiotic group were changed to intravenous treatment due to vomiting.				⊕OOO VERY LOW	CRITICAL
Adverse effects												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	15/244[11]	3/258[12]	RR 5.29 (1.55 to 18.04)	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: UTI, Urinary tract infection; 95% CI, Confidence interval; RR, Relative risk; MD, Mean difference; 99m Tc-DMSA, Technetium-99m-dimercaptosuccinic acid renal scan; VUR, Vesicoureteral reflux; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; RCT, Randomised controlled trial												

1 Strohmeier Y et al. 2014
2 Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as having low risk of bias
3 Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable harm or appreciable benefit
4 Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as having low risk of bias, and 1 RCT which represents 100% weight (the other RCT was not estimable) was at high risk of

bias
[6] Also non-significant results for subgroup with kidney parenchymal damage on initial DMSA scan and the proportion of kidney parenchyma with damage at 6 months (including persistent kidney damage in children with and without VUR)
[7] Downgraded 1 level - at a default minimal important difference of 25% data are consistent with no meaningful difference or appreciable benefit with oral antibiotics[8] Non-significant difference for children with VUR grades 1 and 2 in post hoc subgroup analysis
[9] Downgraded 1 level - size of 95% Confidence interval is very wide
[10] Also non-significant differences for ESR (mm/60 min) and CRP (mg/L)
[11] 13 with diarrhoea or vomiting, 1 with erythema and 1 with leukopenia, none required change in therapy
[12] 1 diarrhoea, 1 erythema and 1 candida, none required change in therapy

Table 28: GRADE profile – Sequential intravenous antibiotics (3 to 4 days) then oral antibiotics compared with intravenous antibiotics (7 to 14 days)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sequential short-course (3 to 4 days) IV antibiotics then oral antibiotics	Longer-course (7 to 14 days) IV antibiotics	Relative (95% CI)	Absolute		
Persistent bacteriuria after treatment												
4[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/149 (2.7%)	6/156 (3.8%)	RR 0.78 (0.24 to 2.55)	8 fewer per 1000 (from 29 fewer to 60 more)	⊕OOO VERY LOW	CRITICAL
Recent UTI within 6 months												
5[1]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	28/498 (5.6%)	29/495 (5.9%)	RR 0.97 (0.58 to 1.62)	2 fewer per 1000 (from 25 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL
Persistent kidney damage at 3 to 6 months (assessed with: all patients with pyelonephritis on 99m-Tc-DMSA scan[5])												
4[1]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	89/377 (23.6%)	86/349 (24.6%)	RR 1.01 (0.8 to 1.29)	2 more per 1000 (from 49 fewer to 71 more)	⊕⊕OO LOW	CRITICAL
Adverse effects (assessed with: gastrointestinal effects)												
2[1]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/85 (11.8%)	8/90 (8.9%)	RR 1.29 (0.55 to 3.05)	26 more per 1000 (from 40 fewer to 182 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: UTI, Urinary tract infection; 95% CI, Confidence interval; RR, Relative risk; 99m Tc-DMSA, Technetium-99m-dimercaptosuccinic acid renal scan; RCT, Randomised controlled trial.												

[1] Strohmeier Y et al. 2014
[2] Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as having low risk of bias, and 1 RCT which represents 86.1% weight in the meta-analysis was at high risk of bias
[3] Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable harm or appreciable benefit
[4] Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as having low risk of bias, and 1 RCT which represents 57.5% weight in the meta-analysis was at high risk of bias
[5] Also NS difference in subgroup analysis for children with renal parenchymal damage on initial DMSA scan, additionally in subgroup analysis NS difference by presence of vesicoureteral reflux, by age group (less than 1 year, age 1 or over or by delay in treatment less than 7 days or 7 days or more in individual kidneys)
[6] Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as having low risk of bias
[7] Downgraded 1 level - at a default minimal important difference of 25% data are consistent with no meaningful difference or appreciable benefit with short duration IV therapy

Table 29: GRADE profile – 3 days versus 10 days of oral antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 days of antibiotics	10 days of antibiotics	Relative (95% CI)	Absolute		
Cure of UTI (assessed with: not defined)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	4/5 (80%)	5/6 (83.3%)	Not reported NICE analysis: RR 0.96 (0.55 to 1.69)	33 fewer per 1000 (from 375 fewer to 575 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: UTI, Urinary tract infection; 95% CI, Confidence interval; RR, Relative risk; RCT, Randomised controlled trial												

[1] Strohmeier et al. 2014
[2] Downgraded 1 level - No RCT was assessed by the Cochrane reviewers as being at low risk of bias
[3] Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable harm or appreciable benefit

Table 30: GRADE profile – single dose injected then oral antibiotics versus oral antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose injected antibiotics then oral antibiotics	Oral antibiotics	Relative (95% CI)	Absolute		
Persistent bacteriuria at 48 hours												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	3/34 (8.8%)[4]	4/35 (11.4%)[5]	RR 0.77 (0.19 to 3.2)	26 fewer per 1000 (from 93 fewer to 251 more)	⊕OOO VERY LOW	CRITICAL
Treatment failure after 48 hours of therapy												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	4/34 (11.8%)[4]	5/35 (14.3%)[5]	RR 0.82 (0.24 to 2.81)	26 fewer per 1000 (from 109 fewer to 259 more)	⊕OOO VERY LOW	CRITICAL
Recurrent UTI within 1 month												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	not estimable	none	0/34 (0%)	0/35 (0%)	Not estimable	Not estimable	⊕⊕OO LOW	CRITICAL
Adverse effects (assessed with: total adverse effects[6])												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	4/34 (11.8%)	3/35 (8.6%)	RR 1.37 (0.33 to 5.68)	32 more per 1000 (from 57 fewer to 401 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: UTI, Urinary tract infection; 95% CI, Confidence interval; RR, Relative risk; RCT, Randomised controlled trial												

[1] Strohmeier Y et al. 2014
[2] Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as being at low risk of bias
[3] Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable harm or appreciable benefit
[4] Ceftriaxone/co-trimoxazole

[5] Co-trimoxazole
[6] also non-significant result for gastrointestinal adverse events

Table 31: GRADE profile – ampicillin suppositories versus oral ampicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ampicillin suppositories	Oral ampicillin	Relative (95% CI)	Absolute		
Persistence of clinical symptoms												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	16/54 (29.6%)	17/51 (33.3%)	RR 0.89 (0.51 to 1.56)	37 fewer per 1000 (from 163 fewer to 187 more)	⊕OOO VERY LOW	CRITICAL
Persistence of bacteriuria												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	18/54 (33.3%)	19/51 (37.3%)	RR 0.89 (0.53 to 1.5)	41 fewer per 1000 (from 175 fewer to 186 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, Confidence interval; RR, Relative risk; RCT, Randomised controlled trial												

[1] Strohmeier Y et al. 2014
[2] Downgraded 1 level - no RCTs were assessed by Cochrane reviewers as having low risk of bias
[3] Downgraded 2 levels - at a default minimal important difference of 25% data are consistent with no meaningful difference, appreciable harm or appreciable benefit

Appendix I: Studies not-prioritised

Study reference	Reason for not prioritising
Bocquet N, Sergent A, Aline , J et al. (2012) Randomized trial of oral versus sequential IV/oral antibiotic for acute pyelonephritis in children. Pediatrics 129(2), e269-75	RCT included in a systematic review that has been prioritised (Strohmeier et al. 2014)
Coats J, Rae N, Nathwani D (2013) What is the evidence for the duration of antibiotic therapy in Gram-negative bacteraemia caused by urinary tract infection? A systematic review of the literature. Journal of global antimicrobial resistance 1(1), 39-42	Lower quality systematic review (includes lower quality RCTs)
Ebrahimzadeh A, Saadatjoo SA, Tabrizi AA (2010) Comparing ceftriaxone and cefazolin for treatment of adult acute pyelonephritis; a clinical trial. Iranian Journal of Clinical Infectious Diseases 5(2), 75-79	Systematic review has been prioritised
Golan Y (2015) Empiric therapy for hospital-acquired, Gram-negative complicated intra-abdominal infection and complicated urinary tract infections: a systematic literature review of current and emerging treatment options. BMC infectious diseases 15, 313	Low relevance to current UK practice (doripenem not available in the UK)
Hewitt IK, Zucchetta P, Rigon L et al. (2008) Early treatment of acute pyelonephritis in children fails to reduce renal scarring: data from the Italian Renal Infection Study Trials. Pediatrics 122(3), 486-90	RCT included in a systematic review that has been prioritised (Strohmeier et al. 2014)
Hodson EM, Willis NS, Craig J C (2007) Antibiotics for acute pyelonephritis in children. The Cochrane database of systematic reviews (4), CD003772	More recent systematic review has been prioritised
Klausner HA, Brown P, Peterson J et al. (2007) A trial of levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400 mg and/or 500 mg twice daily for 10 days in the treatment of acute pyelonephritis. Current medical research and opinion 23(11), 2637-45	Systematic review has been prioritised
Montini G, Toffolo A, Zucchetta P et al. (2007) Antibiotic treatment for pyelonephritis in children: multicentre randomised controlled non-inferiority trial. BMJ (Clinical research ed.) 335(7616), 386	RCT included in a systematic review that has been prioritised (Strohmeier et al. 2014)
Neuhaus TJ, Berger C, Buechner K et al. (2008) Randomised trial of oral versus sequential intravenous/oral cephalosporins in children with pyelonephritis. European journal of pediatrics 167(9), 1037-47	RCT included in a systematic review that has been prioritised (Strohmeier et al. 2014)
Neumann I, Moore P (2011) Pyelonephritis (acute) in non-pregnant women. BMJ clinical evidence 2011,	Lower quality systematic review (includes lower quality RCTs)
Sandberg T, Skoog G, Hermansson AB et al. (2012) Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. Lancet (London, and England) 380(9840), 484-90	RCT included in a systematic review that has been prioritised (Eliakim-Raz et al. 2013)
Singh KP, Li G, Mitrani-Gold FS et al. (2013) Systematic review and meta-analysis of antimicrobial treatment effect estimation in complicated urinary tract infection. Antimicrobial agents and chemotherapy 57(11), 5284-90	Lower quality systematic review (includes lower quality RCTs)

Appendix J: Excluded studies

Study reference	Reason for exclusion
Anonymous (2009) The clinical efficacy and safety of intravenous levofloxacin in the treatment of 4888 patients with bacterial infections: a multi-center trial. Zhonghua nei ke za zhi 48(6), 492-6	Non-English language
Anonymous (2014) Antibiotic prophylaxis for vesicoureteric reflux. Journal of Paediatrics and Child Health 50(8), 653	Evidence type
Arguedas A, Cespedes J, Botet FA et al. (2009) Safety and tolerability of ertapenem versus ceftriaxone in a double-blind study performed in children with complicated urinary tract infection, community-acquired pneumonia or skin and soft-tissue infection. International journal of antimicrobial agents 33(2), 163-7	Evidence type
Bocquet N, Sergent Alaoui, A , Jais J P et al. (2012) Randomized trial of oral versus sequential intravenous/oral antibiotic for acute pyelonephritis in children. Annales Francaises de Medecine d'Urgence 2(6), 372-377	Non-English language
Brandstrom P (2011) The swedish reflux trial. Pediatric nephrology (Berlin, and Germany) 26(9), 1733	Population type
Brandstrom P, Esbjorner E, Herthelius M et al. (2010) The Swedish reflux trial in children: I. Study design and study population characteristics. The Journal of urology 184(1), 274-9	Population type
Brandstrom P, Esbjorner E, Herthelius M et al. (2010) The Swedish reflux trial in children: III. Urinary tract infection pattern. The Journal of urology 184(1), 286-91	Population type
Carpenter MA, Hoberman A, Mattoo TK et al. (2013) The RIVUR trial: profile and baseline clinical associations of children with vesicoureteral reflux. Pediatrics 132(1), e34-45	Population type
de Bessa , J, Jr , de Carvalho M, Flavia C et al. (2015) Antibiotic prophylaxis for prevention of febrile urinary tract infections in children with vesicoureteral reflux: a meta-analysis of randomized, controlled trials comparing dilated to nondilated vesicoureteral reflux. The Journal of urology 193(5 Suppl), 1772-7	Population type
Deepalatha C, Deshpande N (2011) A comparative study of phenazopyridine (pyridium) and cystone as shortterm analgesic in uncomplicated urinary tract infection. International Journal of Pharmacy and Pharmaceutical Sciences 3(Suppl. 2), 224-6	Population type
Garin EH, Olavarria F, Garcia N et al. (2006) Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics 117(3), 626-32	Population type
Grady R (2009) Antibiotic prophylaxis in the management of vesicoureteral reflux. Current urology reports 10(2), 88-9	Evidence type
Gucuk A, Burgu B, Gokce I et al. (2013) Do antibiotic prophylaxis and/or circumcision change periurethral uropathogen colonization and urinary tract infection rates in boys with VUR?. Journal of pediatric urology 9(6 Pt B), 1131-6	Population type
Hari P, Sarin Y K, Mathew J L (2014) Antimicrobial prophylaxis for children with vesicoureteral reflux. Indian Pediatrics 51(7), 571-574	Evidence type
Hari P, Hari S, Sinha A et al. (2015) Antibiotic prophylaxis in the management of vesicoureteric reflux: a randomized double-blind placebo-controlled trial. Pediatric nephrology (Berlin, and Germany) 30(3), 479-86	Population type
Hodson EM, Wheeler DM, Vimalchandra D et al. (2007) Interventions for primary vesicoureteric reflux. The Cochrane database of systematic reviews (3), CD001532	Population type

Study reference	Reason for exclusion
Holmdahl G, Brandstrom P, Lackgren G et al. (2010) The Swedish reflux trial in children: II. Vesicoureteral reflux outcome. The Journal of urology 184(1), 280-5	Population type
Iakovlev S, Suvorova M, Kolendo S et al. (2014) [Clinical efficacy of the antimicrobial drug furamag in nosocomial urinary tract infections]. Terapevticheski arkhiv 86(10), 65-72	Non-English language
Keren R, Carpenter MA, Hoberman A at al. (2008) Rationale and design issues of the Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR) study. Pediatrics 122 Suppl 5, S240-50	Population type
Liu Y-B, Lu X, Huang L (2007) A muticenter, double-blind, randomized clinical trial of parenteral cefepime in the treatment of acute bacterial infections.. Chin J Antibiot 32, 367-370	Non-English language
Martini BC (2016) Ceftolozane/tazobactam is more effective than levofloxacin. Krankenhauspharmazie 37(1), 29	Non-English language
Montini G, Rigon L, Zucchetta P et al. (2008) Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. Pediatrics 122(5), 1064-71	Intervention type
Montini G, Tullus K, Hewitt I (2011) Febrile urinary tract infections in children. The New England journal of medicine 365(3), 239-50	Evidence type
Monmaturapoj T, Montakantikul P, Mootsikapun P et al. (2012) A prospective, randomized, double dummy, placebo-controlled trial of oral cefditoren pivoxil 400mg once daily as switch therapy after intravenous ceftriaxone in the treatment of acute pyelonephritis. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases 16(12), e843-9	Population type
Nagler EV, Williams G, Hodson EM et al. (2011) Interventions for primary vesicoureteric reflux. The Cochrane database of systematic reviews (6), CD001532	Population type
Nordenstrom J, Holmdahl G, Brandstrom P et al. (2016) The Swedish infant high-grade reflux trial: Study presentation and vesicoureteral reflux outcome. Journal of pediatric urology ,	Population type
Peng F-YJ, Wang S (2008) A multicenter, randomized controlled, double-blind clinical trial of piperacillin/tazobactam(4:1) in the treatment of bacterial infections. Chin J Antibiot 33, 114-120	Non-English language
Piccoli GB, Consiglio V, and Colla L et al. (2006) Antibiotic treatment for acute 'uncomplicated' or 'primary' pyelonephritis: a systematic, 'sematic revision'. . Int J Antimicrob Agents 28(suppl 1), S49-S63	Intervention type
Redman R, Damiao R, Kotey P et al. (2010) Safety and efficacy of intravenous doripenem for the treatment of complicated urinary tract infections and pyelonephritis. Journal of chemotherapy (Florence, and Italy) 22(6), 384-91	Intervention type
Roussey-Kesler G, Gadjos V, Idres N et al. (2008) Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. The Journal of urology 179(2), 674-679	Population type
Shaikh N, Hoberman A, Keren R et al. (2016) Predictors of Antimicrobial Resistance among Pathogens Causing Urinary Tract Infection in Children. The Journal of pediatrics 171, 116-21	Population type
Vazquez J, Gonzalez PL, Lipka J et al. (2011) Efficacy, safety and tolerability of ceftazidime/NXL104 vs. imipenem cilastatin in the treatment of complicated urinary tract infections in hospitalised adults. Clinical microbiology and infection 17, S438	Evidence type

Study reference	Reason for exclusion
Wagenlehner FME, Naber K G (2016) Studying ceftazidime-avibactam in selected populations. The Lancet Infectious Diseases 16(6), 621-623	Evidence type

