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Antibiotics for acute pyelonephritis in children (Review)

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[Intervention Review]

Antibiotics for acute pyelonephritis in children

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ABSTRACT

Background

Urinary tract infection (UTI) is one of the most common bacterial infections in infants. The most severe form of UTI is acute pyelonephritis, which results in significant acute morbidity and may cause permanent kidney damage. There remains uncertainty regarding the optimum antibiotic regimen, route of administration and duration of treatment. This is an update of a review that was first published in 2003 and updated in 2005 and 2007.

Objectives

To evaluate the benefits and harms of antibiotics used to treat children with acute pyelonephritis. The aspects of therapy considered were 1) different antibiotics, 2) different dosing regimens of the same antibiotic, 3) different duration of treatment, and 4) different routes of administration.

Search methods

We searched the Cochrane Renal Group's Specialised Register, CENTRAL, MEDLINE, EMBASE, reference lists of articles and conference proceedings without language restriction to 10 April 2014.

Selection criteria

Randomised and quasi-randomised controlled trials comparing different antibiotic agents, routes, frequencies or durations of therapy in children aged 0 to 18 years with proven UTI and acute pyelonephritis were selected.

Data collection and analysis

Four authors independently assessed study quality and extracted data. Statistical analyses were performed using the random-effects model and the results expressed as risk ratio (RR) for dichotomous outcomes or mean difference (MD) for continuous data with 95% confidence intervals (CI).

Main results

This updated review included 27 studies (4452 children). This update included evidence from three new studies, and following re-evaluation, a previously excluded study was included because it now met our inclusion criteria.

Risk of bias was assessed as low for sequence generation (12 studies), allocation concealment (six studies), blinding of outcome assessors (17 studies), incomplete outcome reporting (19 studies) and selective outcome reporting (13 studies). No study was blinded for participants

or investigators. The 27 included studies evaluated 12 different comparisons. No significant differences were found in duration of fever (2 studies, 808 children: MD 2.05 hours, 95% CI -0.84 to 4.94), persistent UTI at 72 hours after commencing therapy (2 studies, 542 children: RR 1.10, 95% CI 0.07 to 17.41) or persistent kidney damage at six to 12 months (4 studies, 943 children: RR 0.82, 95% CI 0.59 to 1.12) between oral antibiotic therapy (10 to 14 days) and intravenous (IV) therapy (3 days) followed by oral therapy (10 days). Similarly, no significant differences in persistent bacteriuria at the end of treatment (4 studies, 305 children: RR 0.78, 95% CI 0.24 to 2.55) or persistent kidney damage (4 studies, 726 children: RR 1.01, 95% CI 0.80 to 1.29) were found between IV therapy (three to four days) followed by oral therapy and IV therapy (seven to 14 days). No significant differences in efficacy were found between daily and thrice daily administration of aminoglycosides (1 study, 179 children, persistent clinical symptoms at three days: RR 1.98, 95% CI 0.37 to 10.53). Adverse events were mild and uncommon and rarely resulted in discontinuation of treatment.

Authors' conclusions

This updated review increases the body of evidence that oral antibiotics alone are as effective as a short course (three to four days) of IV antibiotics followed by oral therapy for a total treatment duration of 10 to 14 days for the treatment of acute pyelonephritis in children. When IV antibiotics are given, a short course (two to four days) of IV therapy followed by oral therapy is as effective as a longer course (seven to 10 days) of IV therapy. If IV therapy with aminoglycosides is chosen, single daily dosing is safe and effective. Insufficient data are available to extrapolate these findings to children aged less than one month of age or to children with dilating vesicoureteric reflux (grades III-V). Further studies are required to determine the optimal total duration of antibiotic therapy required for acute pyelonephritis.

PLAIN LANGUAGE SUMMARY

Are oral antibiotics as effective as a combination of injected and oral antibiotics for kidney infections in children?

Acute pyelonephritis refers to infection of the kidneys and is the most severe form of urinary tract infection (UTI). Acute pyelonephritis causes high fever, vomiting, stomach pain, irritability and poor feeding in infants.

We wanted to find out if oral antibiotics were as effective as combined oral and injected antibiotics to treat children for kidney infection. This review updates our previous investigations published in 2003, 2005 and 2007. This review included evidence from 27 studies that involved 4452 children. The last literature search date was April 2014. This update included evidence from three new studies and from one study that was previously excluded.

Review results suggested that children aged over one month with acute pyelonephritis can be treated effectively with oral antibiotics (cefixime, ceftibuten or amoxicillin/clavulanic acid) or with short courses (two to four days) of intravenous (IV) therapy followed by oral therapy. If IV therapy with aminoglycosides is needed, single daily dosing is safe and effective.

Summary of findings for the main comparison. Oral versus IV followed by oral (11 days) therapy for acute pyelonephritis in children

Oral versus IV followed by oral (11 days) therapy for acute pyelonephritis in children

Patient or population: children with acute pyelonephritis
Intervention: oral versus IV followed by oral (11 days) therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Oral	IV followed by oral (11 days) therapy				
Time to fever resolution (hours)		The mean time to fever resolution (hours) in the intervention groups was **2.05 higher** (0.84 lower to 4.94 higher)		808 (2)	⊕⊕⊕⊖ **moderate**[1]	
Renal parenchymal damage at 6 to 12 months: all included children with acute pyelonephritis DMSA scans Follow-up: 6 to 12 months	**Study population**		**RR 0.82** (0.59 to 1.12)	943 (4)	⊕⊕⊕⊖ **moderate**[2]	
	224 per 1000	**184 per 1000** (132 to 251)				
	Moderate					
	313 per 1000	**257 per 1000** (185 to 351)				
Renal parenchymal damage at 6 to 12 months: children with renal parenchymal damage on initial DMSA Follow-up: 6 to 12 months	**Study population**		**RR 0.79** (0.61 to 1.03)	681 (4)	⊕⊕⊕⊖ **moderate**[3]	
	320 per 1000	**253 per 1000** (195 to 330)				
	Moderate					
	382 per 1000	**302 per 1000** (233 to 393)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Wide confidence intervals due to large standard deviations around the mean durations of fever
[2] Large number of patients excluded because of lack of follow-up DMSA scans
[3] No explanation was provided

Summary of findings 2. Short duration (3 to 4 days) versus long duration (7 to 14 days) IV therapy for acute pyelonephritis in children

Short duration (3 to 4 days) versus long duration (7 to 14 days) IV therapy for acute pyelonephritis in children

Patient or population: children with acute pyelonephritis
Intervention: short duration (3 to 4 days) versus long duration (7 to 14 days) IV therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Short duration (3 to 4 days)	Long duration (7 to 14 days) IV therapy				
Persistent bacteriuria after treatment	**Study population**		**RR 0.78** (0.24 to 2.55)	305 (4)	⊕⊕⊝⊝ **low**[1,2]	
	38 per 1000	**30 per 1000** (9 to 98)				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Recurrent UTI within 6 months	**Study population**		**RR 0.97** (0.58 to 1.62)	993 (5)	⊕⊕⊕⊝ **moderate**[1]	
	59 per 1000	**57 per 1000** (34 to 95)				

	Moderate				
	56 per 1000	**54 per 1000** (32 to 91)			
Persistent renal damage at 3 to 6 months: all included children with acute pyelonephritis	**Study population**		**RR 1.01** (0.8 to 1.29)	726 (4)	⊕⊕⊕⊖ **moderate**[1,3]
	246 per 1000	**249 per 1000** (197 to 318)			
	Moderate				
	257 per 1000	**260 per 1000** (206 to 332)			
Persistent renal damage at 3 to 6 months: children with initial renal parenchymal damage on initial DMSA scan Follow-up: 6-12 months	**Study population**		**RR 1.1** (0.84 to 1.45)	315 (3)	⊕⊕⊕⊖ **moderate**[1,3]
	357 per 1000	**393 per 1000** (300 to 518)			
	Moderate				
	327 per 1000	**360 per 1000** (275 to 474)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Unclear or inadequate allocation concealment
[2] Small number of patients and events leading to wide confidence intervals
[3] In several studies, more than 10% patients lost to follow-up or did not have follow-up DMSA scans

Summary of findings 3. Different dosing regimens of aminoglycosides (daily versus 8 hourly) for acute pyelonephritis in children

Different dosing regimens of aminoglycosides (daily versus 8 hourly) for acute pyelonephritis in children

Patient or population: children with acute pyelonephritis
Intervention: different dosing regimens of aminoglycosides (daily versus 8 hourly)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Daily dose	8 hourly dose				
Persistent bacteriuria after 1 to 3 days of treatment	**Study population**		**RR 1.05** (0.15 to 7.27)	435 (3)	⊕⊕⊝⊝ **low**[1,2]	
	9 per 1000	**10 per 1000** (1 to 67)				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Hearing impairment following treatment	**Study population**		**RR 2.83** (0.33 to 24.56)	271 (3)	⊕⊕⊝⊝ **low**[1,2]	
	0 per 1000	**0 per 1000** (0 to 0)				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Increase in serum creatinine during treatment	**Study population**		**RR 0.75** (0.2 to 2.82)	419 (3)	⊕⊕⊝⊝ **low**[1,2]	
	25 per 1000	**19 per 1000** (5 to 70)				
	Moderate					
	25 per 1000	**19 per 1000** (5 to 70)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Unclear allocation concealment in two of three studies
[2] Few events resulting in wide confidence intervals

Summary of findings 4. Agent: Third generation cephalosporin versus other antibiotic for acute pyelonephritis in children

Agent: Third generation cephalosporin versus other antibiotic for acute pyelonephritis in children

Patient or population: children with acute pyelonephritis
Intervention: third generation cephalosporin versus other antibiotic

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Antibiotic	Third generation cephalosporin				
Persistent bacteriuria	**Study population**		**RR 2.41** (0.98 to 5.93)	439 (3)	⊕⊕⊝⊝ **low**[1,2]	
	34 per 1000	**81 per 1000** (33 to 199)				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Recurrent UTI after end of therapy	**Study population**		**RR 1.23** (0.32 to 4.74)	491 (4)	⊕⊕⊝⊝ **low**[1,2]	
	18 per 1000	**22 per 1000** (6 to 87)				
	Moderate					
	8 per 1000	**10 per 1000** (3 to 38)				

Persistent symptoms after end of treatment	**Study population**		**RR 0.28** (0.13 to 0.62)	471 (3)	⊕⊕⊖⊖ **low**[1,3]
	104 per 1000	**29 per 1000** (14 to 64)			
	Moderate				
	0 per 1000	**0 per 1000** (0 to 0)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Unclear allocation in several studies
[2] Few events leading to imprecision
[3] Meta-analysis dominated by single trial and results inconsistent with bacteriologic results

BACKGROUND

Description of the condition

The urinary tract is a common site of bacterial infection in infants and young children. Pooled prevalence data demonstrate that approximately 7% of girls and boys are diagnosed with at least one urinary tract infection (UTI) by the age of 19 years (Shaikh 2008). Girls are more susceptible to UTIs than boys after the first six months of life with a prevalence of 11% in girls and 4% in boys (Brkic 2010). UTI is defined by the presence of bacteria in urine (bacteriuria), which when cultured is measured in colony forming units/mL (CFU/mL) of uncentrifuged urine. The diagnosis of UTI in children is generally confirmed by the pure growth of a bacteria of greater than 10^3 CFU/mL from a suprapubic aspirate, 10^4 CFU/mL from a bladder catheter specimen and 10^5 CFU/mL from non-invasive collection methods (clean catch and urinary bag specimens) (Bhat 2011).

UTIs can be clinically grouped into asymptomatic bacteriuria, cystitis and acute pyelonephritis.

- Asymptomatic bacteriuria is the presence of bacteriuria without clinical signs and symptoms.
- Cystitis is a UTI limited to the urethra and bladder and is seen most commonly in girls over two years of age. It presents with localising symptoms of dysuria (pain when passing urine), frequency, urgency, cloudy urine and lower abdominal discomfort. Pyuria (white cells in the urine) and haematuria (blood in the urine) may also be found.
- Acute pyelonephritis refers to infection of the kidneys, and is the most severe form of UTI in children. Clinically, this is associated with systemic features such as high fever, malaise, vomiting, abdominal and loin pain and tenderness, poor feeding and irritability in infants. Together with urine culture, diagnosis may be assisted by imaging using technetium 99m labelled dimercaptosuccinic acid (DMSA) renal scan and markers of inflammation in the blood such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).
- Acute pyelonephritis is associated with significant short-term morbidity, including shock and septicaemia, especially in infants. Acute kidney parenchymal injury has been demonstrated on DMSA scan in about 60% of children shortly after UTI diagnosis (Shaikh 2010). Permanent kidney damage may occur following acute pyelonephritis and is more frequent in children who have multiple episodes or who have vesicoureteric reflux (VUR) (Shaikh 2010; Smellie 1985). Serial DMSA scans of children after a first episode of acute pyelonephritis show that 15% of children with acute changes on DMSA scans have permanent kidney scarring at follow up (Shaikh 2010). However, the long term significance of kidney damage following acute pyelonephritis is debatable. In children with previously normal kidneys, the amount of damage is small and unlikely to cause disease (Salo 2011; Toffolo 2012).

Description of the intervention

A wide variety of antibiotic agents have been used to treat acute pyelonephritis in children. Antibiotics that have been used include aminoglycosides, cephalosporins, penicillins and trimethoprim/sulphamethoxazole (TMP/SMX). Historically, children who are judged by clinicians to be in poor general condition are given parenteral antibiotics and those who appear less sick have been given oral antibiotics, without clarity whether one route of administration is superior. An antibiotic course of seven to 14 days is generally recommended although the optimal duration of therapy is not known. Shorter courses may be associated with treatment failure while longer courses may unnecessarily expose children to the adverse effects of treatment. This review evaluated antibiotic therapies used to treat acute pyelonephritis, with consideration of different antibiotic agents, different dosing regimens of the same antibiotic, different durations of treatment and different routes of administration.

How the intervention might work

Antibiotics work in the treatment of acute pyelonephritis by eliminating bacterial infection in the urinary tract. The purpose of antibiotic therapy is to eradicate and prevent progressive infection and its consequences, including shock and septicaemia, reduce acute kidney injury and resolve the acute clinical symptoms of infection. The efficacy of treatment depends on using the antibiotic(s) to which the bacteria is sensitive. While the results of antibiotic sensitivity testing are pending, initial treatment is chosen on an empiric basis to cover the most likely cause of infection.

Why it is important to do this review

Acute pyelonephritis is a common serious infection in children. Nonetheless, there remains no consensus on the most effective antibiotic regimen for the treatment of acute pyelonephritis. There is also uncertainty regarding the optimal route of administration of antibiotic therapy. Previously, most authorities recommended commencing antibiotic therapy by the parenteral route. The most recent guidelines however recommend initial treatment with oral antibiotics for children older than two months (AAP 2011) or three months of age (NICE 2007) unless children are considered to be too unwell or unable to take oral antibiotics. This is advantageous because oral therapy is more convenient and does not require hospital admission, thereby reducing costs. There is further uncertainty about the optimal duration of antibiotic therapy. Currently, the recommended duration of therapy varies from seven to 14 days.

This review update was necessary to provide additional information about the optimum antibiotic regimens, route of administration and duration of treatment for acute pyelonephritis in children and about adverse effects of treatment.

OBJECTIVES

To evaluate the benefits and harms of antibiotics used to treat children with acute pyelonephritis. The aspects of therapy considered were:

1. different antibiotics
2. different dosing regimens of the same antibiotic
3. different duration of treatment
4. different routes of administration.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in which antibiotics were used in the treatment of children (birth to 18 years) with acute pyelonephritis were included. Where studies included both children with acute pyelonephritis and those with cystitis, these were included if data for participants with acute pyelonephritis could be extracted separately; otherwise, these studies were excluded.

Types of participants

Inclusion criteria

Children from birth to 18 years with acute pyelonephritis treated either in hospital or as outpatients with antibiotics were included. For this review, the diagnosis of acute pyelonephritis required UTI (as specified in the included studies but generally requiring a bacterial growth on urine culture of more than 10^5 CFU/mL or 10^8 CFU/L) with at least one symptom or sign of systemic illness such as fever, loin pain or toxicity and additional diagnostic criteria as defined by the authors of the included studies. Children with previously diagnosed urinary tract abnormalities including VUR or previous UTI could be included.

Exclusion criteria

Patients considered to have asymptomatic bacteriuria or cystitis (UTI as defined in Inclusions with no symptom or sign of systemic illness) were excluded.

Types of interventions

- Different antibiotic agents
- IV antibiotic versus oral antibiotic
- Different doses or duration or both of the same antibiotic
- Antibiotic versus placebo, no therapy or alternative non-antibiotic therapy.

Types of outcome measures

Primary outcomes

Short-term outcome measures.

- Duration of fever
- Persistent symptoms (e.g. UTI at 72 hours; inflammatory markers at 72 hours (ESR, WCC, CRP)
- Acute kidney parenchymal damage on DMSA scan
- Length of hospital stay for inpatients
- Persistent bacteriuria after completion of antibiotics
- Recurrent UTI
- Adverse effects of treatment including minor (e.g. vomiting, discomfort from IV cannula) and major (e.g. anaphylaxis, hearing impairment)
- Economic costs of treatment (if data available).

Secondary outcomes

Long-term outcome measures.

- Persistent kidney damage (as defined by authors of included studies)
- Hypertension
- Chronic kidney disease.

Search methods for identification of studies

Electronic searches

For the 2014 update, we searched the Cochrane Renal Group's Specialised Register through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the Cochrane Renal Group.

See Appendix 1 for search terms used in strategies for this review update.

For previous search strategies please refer to our earlier reviews (Bloomfield 2003; Bloomfield 2005; Hodson 2007).

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies relevant to the review. Titles and abstracts were screened independently by four authors, who discarded studies that were not applicable. However, studies and reviews that included relevant data or information on studies were retained initially. Four authors independently assessed retrieved abstracts, and if necessary the full text, to determine which studies satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by four authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data was used in the analyses. Where relevant outcomes were only published in earlier versions those data were used. Any discrepancy between published versions was highlighted.

Assessment of risk of bias in included studies

The following items were independently assessed by four authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
  - Participants and personnel
  - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (persistent bacteriuria, recurrent UTI, persistent clinical symptoms, presence of kidney parenchymal damage, adverse effects) results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (duration of fever, inflammatory markers, extent of kidney parenchymal damage), the mean difference (MD) was used.

Unit of analysis issues

The unit of analysis was the study participant and not events, that is, the number of children with acute pyelonephritis rather than the number of episodes of acute pyelonephritis per child.

Dealing with missing data

Where data were missing or unclear, we contacted the original authors of studies to request additional data. An attempt to obtain the preliminary results of the terminated study (NCT00724256) was made by contacting the lead investigator. We did not impute missing data.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi squared test on N-1 degrees of freedom with an alpha of 0.1 used for statistical significance and the I^2 statistic (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

We planned to assess publication bias by constructing funnel plots; however, there were insufficient data in each meta-analysis to enable this analysis to be conducted.

Data synthesis

Data were pooled using the random-effects model but the fixed-effect model was also used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was planned to explore possible sources of heterogeneity (participants, treatments and study quality) but could not be undertaken because of the small number of studies for each comparison. Heterogeneity among participants could be related to age (infants versus adolescents) and pre-existing renal tract pathology. Heterogeneity in treatment could be related to inpatient versus outpatient management, prior antibiotics used and the antibiotic, dose, duration and route of administration of therapy.

Sensitivity analysis

Sensitivity analysis was planned to identify individual studies that were contributing to significant heterogeneity (I^2 value greater than 75%) but the I^2 values of all meta-analyses were less than 50% so sensitivity analysis was not undertaken.

RESULTS

Description of studies

Results of the search

First version published 2003

The initial search in September 2002 identified 1520 titles and abstracts of which 51 were screened. We found that 16 parallel RCTs (16 reports) involving 1872 children fulfilled the eligibility criteria and were included in the review. We excluded 11 studies (11 reports) (Bloomfield 2003).

Review updates published 2005 and 2007

A search in June 2004 identified two additional studies (three reports) (Chong 2003; Montini 2007). A total of 18 studies (19 reports) involving 2612 children were included in our 2005 review update (Bloomfield 2005).

A search from 2004 to July 2007 identified 26 reports of which 16 were excluded (not randomised, mixed populations or wrong interventions). We included five new studies (nine reports) (Banfi 1993; Cheng 2006; Fujii 1987; Neuhaus 2008; Noorbakhsh 2004). The final results of the multicentre study by Montini 2007 were published and included in this update. We included 23 studies (29 reports) that involved 3407 children in the 2007 update (Hodson 2007).

Review update 2014

A search in 10 April 2014 identified 32 reports. In addition, a previously excluded study was re-evaluated and included because it had been excluded incorrectly based on how outcomes were reported. Khan 1981 had been previously excluded because results

were reported as episodes of acute pyelonephritis rather than number of patients with an episode of acute pyelonephritis. We excluded 17 studies (17 reports) and identified one eligible study that was terminated (see Characteristics of ongoing studies); contact with the triallists confirmed that no results were available (NCT00724256). We found that nine new records were further reports of four previously included studies (Benador 2001; Cheng 2006; Montini 2007; Neuhaus 2008). Reports relating to Benador 2001, Cheng 2006 and Montini 2007 did not provide any new data; however, the final results of Neuhaus 2008 (two new reports) were published in September 2008 and results were included in this review update. Four reports were of three newly identified studies (Bocquet 2012; Bouissou 2008; Marild 2009). This update included 27 studies (42 reports) that involved 4452 children.

See Figure 1.

Figure 1. Study flow diagram.

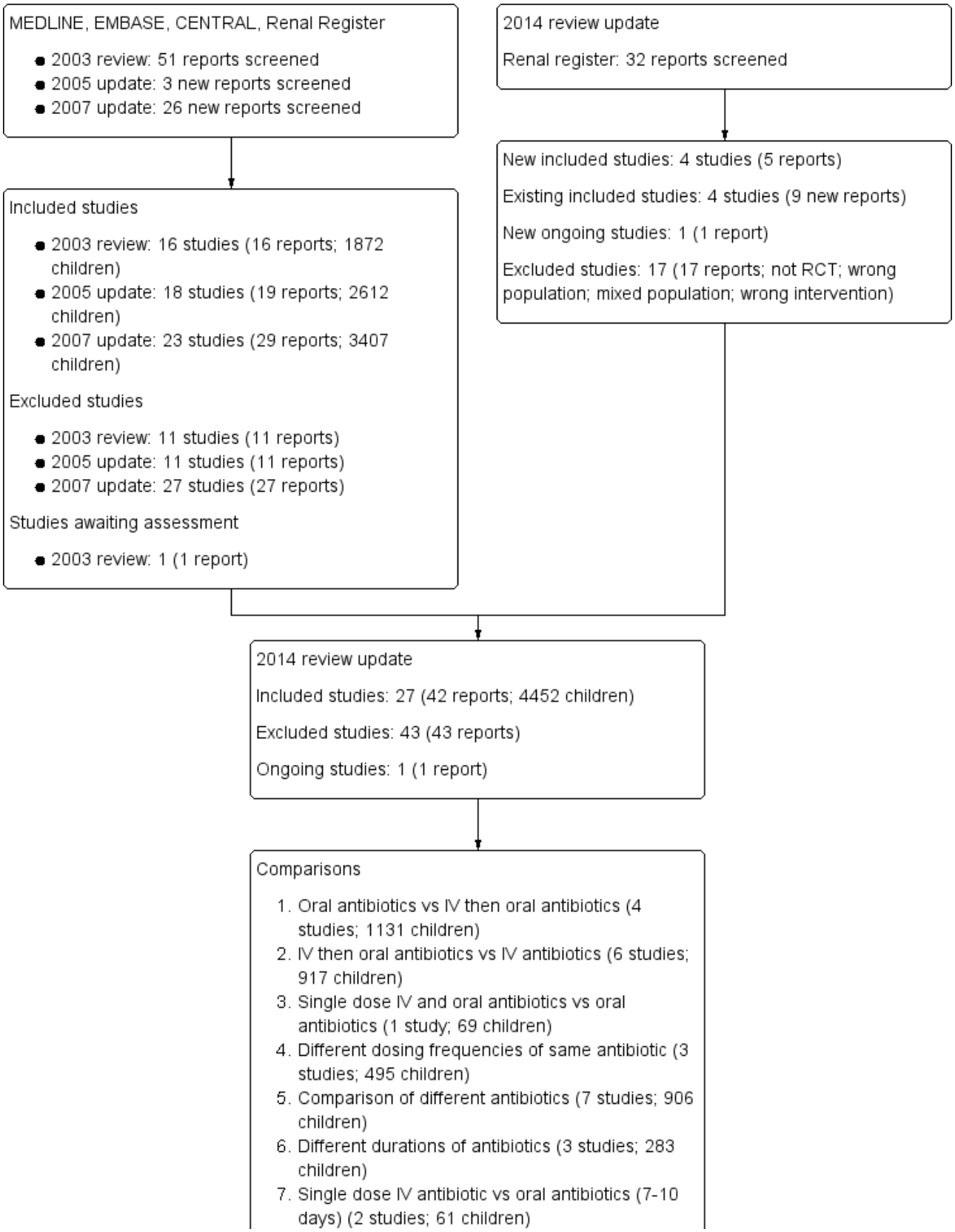
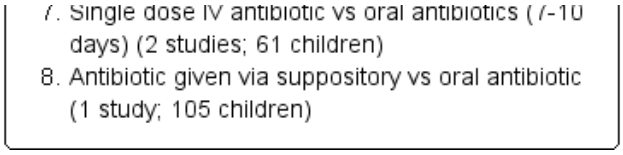


Figure 1. (Continued)



Included studies

The characteristics of the 27 included studies are summarised in Characteristics of included studies.

Participants

Studies recruited participants from the ages of two weeks to 16 years. Three studies did not specify age range (Bakkaloglu 1996; Levtchenko 2001; Pylkkänen 1981).

Healthcare settings

- Children received treatment while inpatients in seven studies (Bakkaloglu 1996; Carapetis 2001; Chong 2003; Fujii 1987; Kafetzis 2000; Montini 2007; Vigano 1992).
- Children were treated as outpatients only in four studies (Baker 2001; Khan 1981; Pylkkänen 1981; Repetto 1984).
- Children received treatment in both in- and outpatient settings in 16 studies (Banfi 1993; Benador 2001; Bocquet 2012; Bouissou 2008; Cheng 2006; Fischbach 1989; Francois 1997; Hoberman 1999; Grimwood 1988; Levtchenko 2001; Marild 2009; Neuhaus 2008; Noorbakhsh 2004; Schaad 1998; Toporovski 1992; Vilaichone 2001).

Urine collection

- All urine specimens were collected by suprapubic aspiration, catheter or midstream specimens in 14 studies (Banfi 1993; Baker 2001; Bouissou 2008; Carapetis 2001;Chong 2003; Grimwood 1988; Hoberman 1999; Kafetzis 2000; Khan 1981; Neuhaus 2008; Pylkkänen 1981; Repetto 1984; Toporovski 1992; Vigano 1992).
- Specimens were obtained by strap-on bag collection in nine studies (Benador 2001; Bocquet 2012; Cheng 2006; Levtchenko 2001; Marild 2009; Montini 2007; Noorbakhsh 2004; Schaad 1998; Vilaichone 2001).
- The method of urine collection was not specified in four studies (Bakkaloglu 1996; Fischbach 1989; Francois 1997; Fujii 1987).

Diagnosis

- All participants had acute pyelonephritis in 22 studies (Baker 2001; Bakkaloglu 1996; Benador 2001; Bocquet 2012; Bouissou 2008; Carapetis 2001; Cheng 2006; Chong 2003; Fischbach 1989; Francois 1997; Fujii 1987; Hoberman 1999; Kafetzis 2000; Levtchenko 2001; Marild 2009; Montini 2007; Neuhaus 2008; Noorbakhsh 2004; Schaad 1998; Toporovski 1992; Vigano 1992; Vilaichone 2001).
- Five studies enrolled children with both acute pyelonephritis and lower UTI (Banfi 1993; Grimwood 1988; Khan 1981; Pylkkänen 1981; Repetto 1984); data from children with acute pyelonephritis, which could be separated, were included in this review.

Definition of acute pyelonephritis

All studies required positive urine culture. Additional criteria required for diagnosis of acute pyelonephritis in children with UTI varied among studies:

- Four studies required fever > 38°C (Baker 2001; Bocquet 2012; Hoberman 1999; Khan 1981).
- Eight required fever and at least one additional clinical feature (Bakkaloglu 1996; Carapetis 2001; Chong 2003; Grimwood 1988; Noorbakhsh 2004; Repetto 1984; Schaad 1998; Toporovski 1992).
- Nine required fever, clinical features and/or laboratory abnormalities (CRP, ESR, white blood count) (Bouissou 2008; Fischbach 1989; Francois 1997; Kafetzis 2000; Levtchenko 2001; Marild 2009; Montini 2007; Pylkkänen 1981; Vigano 1992).
- Three required fever, clinical features and acute kidney parenchymal injury on DMSA scan (Benador 2001; Neuhaus 2008; Vilaichone 2001).
- Five other studies (Bocquet 2012; Chong 2003; Hoberman 1999; Levtchenko 2001; Montini 2007) provided information on the number of children with acute pyelonephritis based on clinical characteristics, who had DMSA abnormalities at study entry.
- One study required fever with computer tomography scan evidence of acute lobular nephronia (Cheng 2006).

Two studies did not report the definition used for acute pyelonephritis (Banfi 1993; Fujii 1987).

Commonly reported exclusion criteria

- Impaired kidney function (12 studies: Carapetis 2001; Chong 2003; Fischbach 1989; Francois 1997; Kafetzis 2000; Khan 1981; Noorbakhsh 2004; Repetto 1984; Schaad 1998; Toporovski 1992; Vigano 1992; Vilaichone 2001).
- Known severe urinary tract abnormality (14 studies: Baker 2001; Benador 2001; Bocquet 2012; Bouissou 2008; Francois 1997; Hoberman 1999; Khan 1981; Levtchenko 2001; Marild 2009; Neuhaus 2008; Noorbakhsh 2004; Repetto 1984; Vigano 1992; Vilaichone 2001).
- Known sensitivity to study medications (17 studies: Banfi 1993; Baker 2001; Benador 2001;Bocquet 2012; Carapetis 2001; Chong 2003; Fischbach 1989; Francois 1997; Hoberman 1999; Kafetzis 2000; Marild 2009; Noorbakhsh 2004; Repetto 1984; Schaad 1998; Toporovski 1992; Vigano 1992; Vilaichone 2001).

Other exclusion criteria

- Recent antibiotic use (10 studies: Banfi 1993; Baker 2001; Bocquet 2012; Chong 2003; Fischbach 1989; Kafetzis 2000; Marild 2009; Montini 2007; Noorbakhsh 2004; Vilaichone 2001).
- Previous UTI (seven studies: Bouissou 2008; Fischbach 1989; Francois 1997; Hoberman 1999; Marild 2009; Montini 2007; Vilaichone 2001).

- Clinical signs of shock at presentation (six studies: Baker 2001; Bocquet 2012; Francois 1997; Hoberman 1999; Montini 2007; Neuhaus 2008).
- Immune compromise (six studies: Banfi 1993; Bouissou 2008; Carapetis 2001; Francois 1997; Noorbakhsh 2004; Schaad 1998).
- Known hearing impairment (four studies: Carapetis 2001; Chong 2003; Kafetzis 2000; Vigano 1992).
- Uncomplicated acute pyelonephritis (APN) (one study: Cheng 2006).

Four studies did not specify any exclusion criteria (Bakkaloglu 1996; Fujii 1987; Grimwood 1988; Pylkkänen 1981).

Study comparisons

The 27 included studies evaluated eight different comparisons.

- Four studies compared oral therapy with short duration IV therapy followed by oral therapy (Bocquet 2012; Hoberman 1999; Montini 2007; Neuhaus 2008).
- In six studies, short duration IV therapy (three to four days) followed by oral therapy was compared with long duration IV therapy (seven to 14 days) (Benador 2001; Bouissou 2008; Francois 1997; Levtchenko 2001; Noorbakhsh 2004; Vilaichone 2001).
- A single dose of parenteral antibiotic added to oral therapy was compared to oral therapy alone in one study (Baker 2001).
- Three studies compared different dosing frequencies of the same antibiotic agents (Carapetis 2001; Chong 2003; Vigano 1992).
- Seven studies compared different antibiotics (Banfi 1993; Bakkaloglu 1996; Fischbach 1989; Kafetzis 2000; Marild 2009; Schaad 1998; Toporovski 1992). Toporovski 1992 included two experimental groups who received different doses of antibiotic. Because treatment response did not differ, experimental group data were combined.
- Three studies compared different durations of antibiotics (Cheng 2006; Khan 1981; Pylkkänen 1981).
- Two studies assessed single dose parenteral therapy against seven to 10 days of oral antibiotic therapy (Grimwood 1988; Repetto 1984).
- One study compared ampicillin suppositories with oral ampicillin (Fujii 1987).

Reported outcomes

Not all studies reported the same outcomes. Table 1shows the outcomes reported for each study comparison.

Excluded studies

We excluded a total of 43 studies because: data from children with acute pyelonephritis could not be separated from those with lower UTI (18), children had lower UTI only (8), antibiotics were studied as prophylactic agents (5), the studies involved ineligible interventions or populations (5) or the study was not randomised (7).

Risk of bias in included studies

The assessment of risk of bias is shown in Figure 2 and Figure 3. Figure 2 shows the proportion of studies assessed as low, high or unclear risk of bias for each risk of bias indicator. Figure 3 shows the risk of bias indicators for individual studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

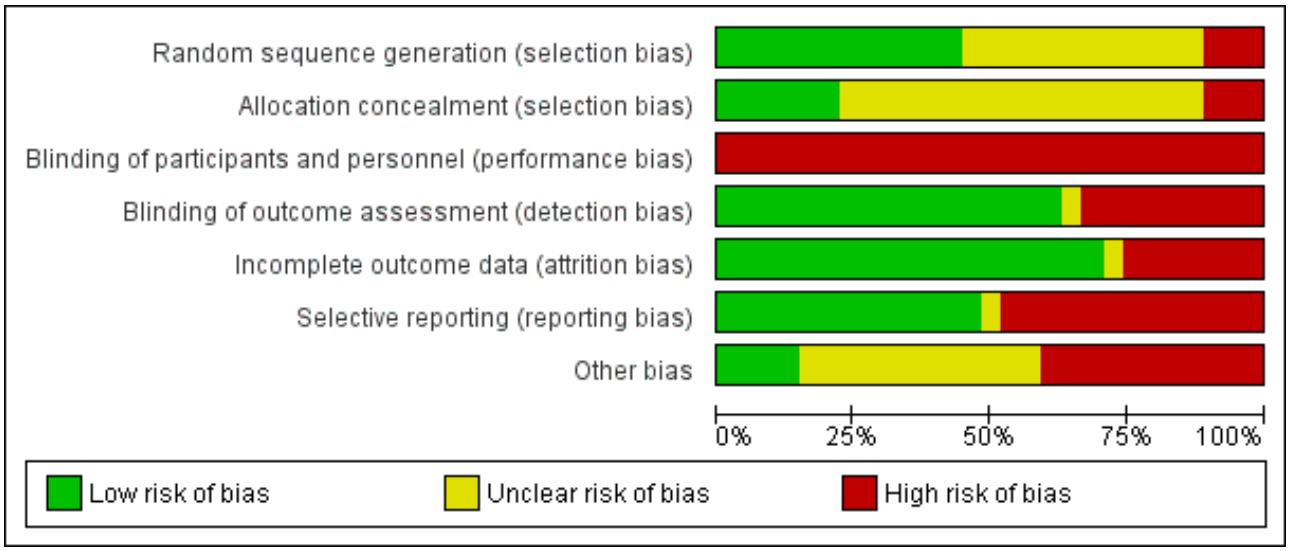


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

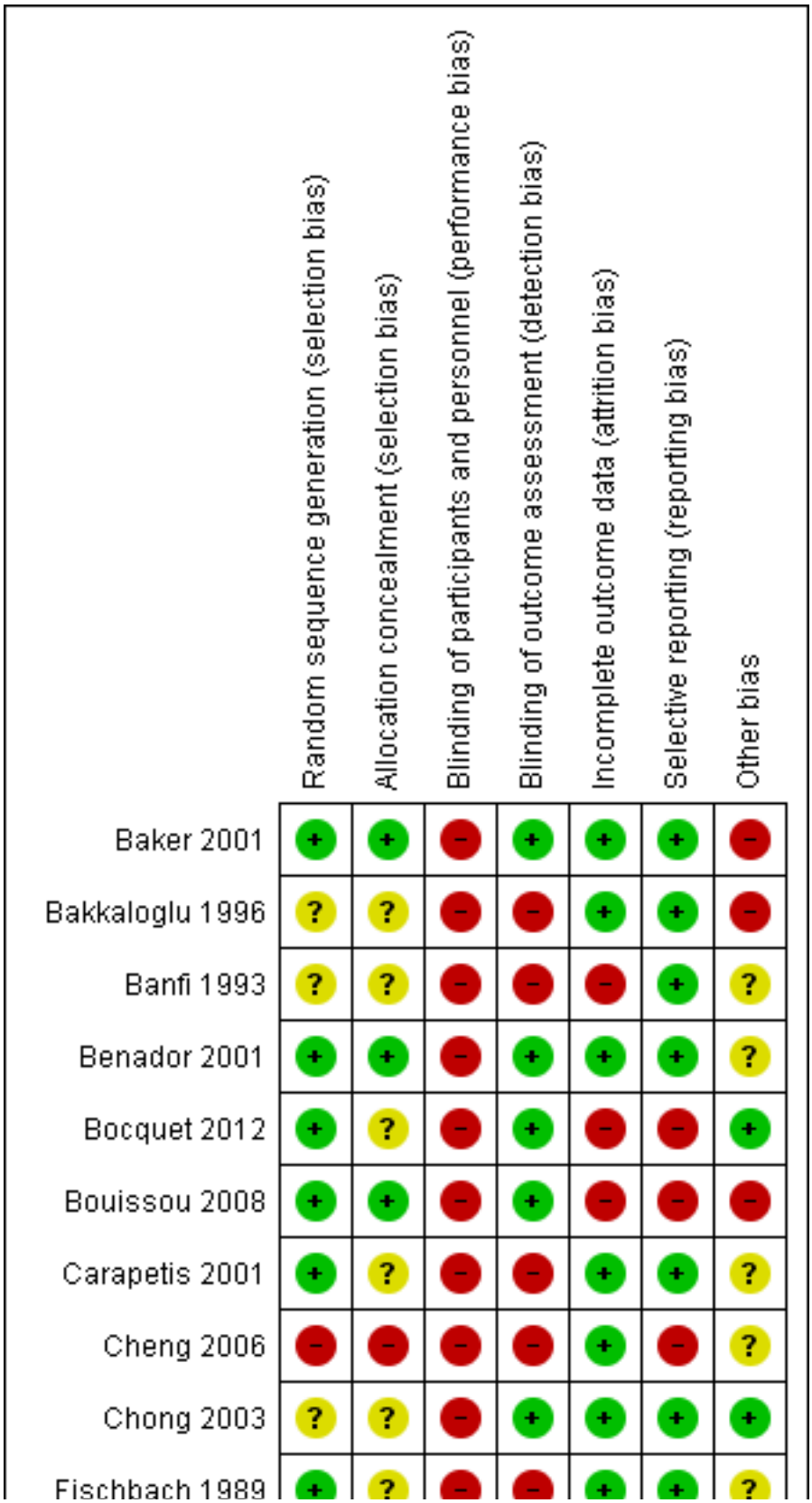
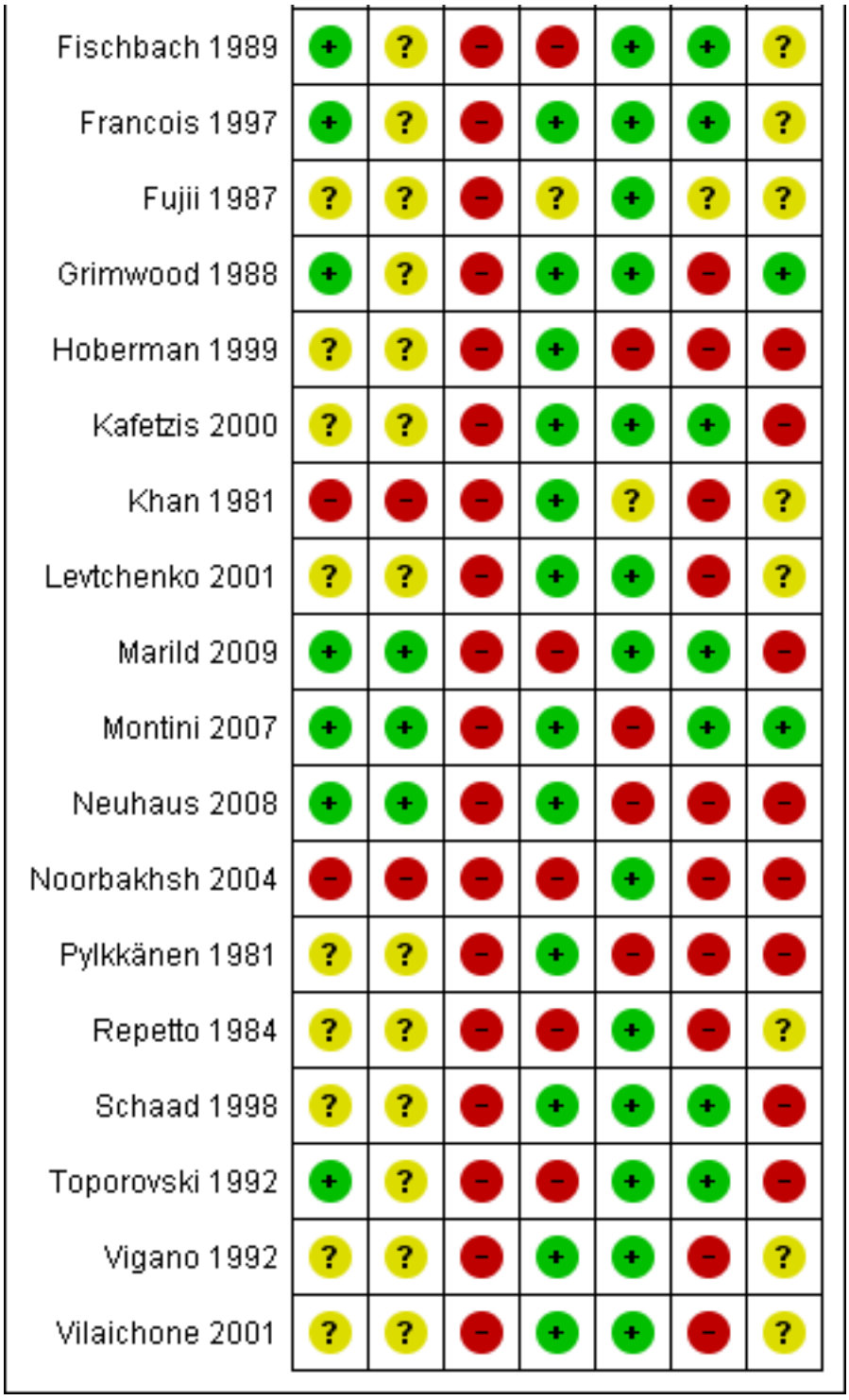


Figure 3. (Continued)



Allocation

Sequence generation was considered to be at low risk of bias in 12 studies (Baker 2001; Benador 2001; Bocquet 2012; Bouissou 2008; Carapetis 2001; Fischbach 1989; Francois 1997; Grimwood 1988; Marild 2009; Montini 2007; Neuhaus 2008; Toporovski 1992) and assessed at high risk in three studies (Cheng 2006; Khan 1981; Noorbakhsh 2004). Randomisation methods were not reported in 12 studies.

Allocation concealment was considered to be at low risk of bias in six studies (Baker 2001; Benador 2001; Bouissou 2008; Marild 2009; Montini 2007; Neuhaus 2008) and high risk in three studies (Cheng 2006; Khan 1981;Noorbakhsh 2004). Allocation concealment was assessed as unclear in 18 studies.

Blinding

Participants and investigators were not blinded in any of the included studies. The absence of blinding was considered to be a high risk of bias because symptom reporting and clinical management could be influenced by knowledge of the treatment group (performance bias). Bakkaloglu 1996 was reported to be double-blinded but antibiotics were administered at different frequencies and no placebos were given.

Outcome assessors (detection bias) were blinded in 17 studies (Baker 2001; Benador 2001; Bocquet 2012; Bouissou 2008; Chong 2003; Francois 1997; Grimwood 1988; Hoberman 1999; Kafetzis 2000; Khan 1981; Levtchenko 2001; Montini 2007; Neuhaus 2008; Pylkkänen 1981; Schaad 1998; Vigano 1992; Vilaichone 2001). Blinding of outcome assessors was not carried out in nine studies (Bakkaloglu 1996; Banfi 1993; Carapetis 2001; Cheng 2006; Fischbach 1989; Marild 2009; Noorbakhsh 2004; Repetto 1984; Toporovski 1992). There was no reporting of outcome assessment blinding in Fujii 1987 (abstract only available).

Incomplete outcome data

Not all studies reported all outcomes. The reported outcomes from each of the included studies are summarised in Table 1. Incomplete outcome data was considered to be at low risk of bias in 19 studies because they reported outcomes in more than 90% of participants (Baker 2001; Bakkaloglu 1996; Benador 2001; Carapetis 2001; Cheng 2006; Chong 2003; Fischbach 1989; Francois 1997; Fujii 1987; Grimwood 1988; Kafetzis 2000; Levtchenko 2001; Marild 2009; Noorbakhsh 2004; Repetto 1984; Schaad 1998; Toporovski 1992; Vigano 1992; Vilaichone 2001). Attrition and exclusion of participants after the randomisation process was considered to be at a high risk of bias in seven studies (Banfi 1993; Bocquet 2012; Bouissou 2008; Hoberman 1999; Montini 2007; Neuhaus 2008; Pylkkänen 1981) and unclear in Khan 1981.

Selective reporting

There were 13 studies that reported bacteriological, clinical and adverse outcomes and were considered at low risk of bias (Baker 2001; Bakkaloglu 1996; Banfi 1993; Benador 2001; Carapetis 2001; Chong 2003; Fischbach 1989; Francois 1997; Kafetzis 2000; Marild 2009; Montini 2007; Schaad 1998; Toporovski 1992). Fujii 1987 was an abstract and did not clearly indicate outcomes investigated. The remaining 13 studies did not report all three types of outcomes and were considered at high risk of bias.

Other potential sources of bias

We assessed that 11 studies were at high risk of bias because they reported receiving funding from pharmaceutical companies (Baker 2001; Banfi 1993; Bouissou 2008; Hoberman 1999; Kafetzis 2000; Marild 2009; Neuhaus 2008; Noorbakhsh 2004; Pylkkänen 1981; Schaad 1998; Toporovski 1992). Four received funding from hospital grants (Bocquet 2012; Chong 2003; Grimwood 1988) or a government grant (Montini 2007) and were considered at low risk of bias. The source of funding in the remaining 12 studies was unclear.

Effects of interventions

See: **Summary of findings for the main comparison** Oral versus IV followed by oral (11 days) therapy for acute pyelonephritis in children; **Summary of findings 2** Short duration (3 to 4 days) versus long duration (7 to 14 days) IV therapy for acute pyelonephritis in children; **Summary of findings 3** Different dosing regimens of aminoglycosides (daily versus 8 hourly) for acute pyelonephritis in children; **Summary of findings 4** Agent: Third generation cephalosporin versus other antibiotic for acute pyelonephritis in children

Because results from random and fixed-effect models did not differ, only results from the random-effects model were reported. Few studies were available for pooling in meta-analyses. No pre-planned subgroup analyses for outcomes according to patient age (infant, child, adolescent) were possible from the available data. Post hoc subgroup analyses were reported for age (less than or greater than one year of age, Benador 2001) and VUR (Benador 2001; Hoberman 1999; Vilaichone 2001) and delay in treatment (less than or greater than seven days, Levtchenko 2001).

Oral therapy versus sequential IV therapy and oral therapy

We found four studies (Bocquet 2012; Hoberman 1999; Montini 2007; Neuhaus 2008) involving 1131 children compared oral antibiotics (cefixime, ceftibuten or amoxicillin/clavulanic acid) for 10 to 14 days with IV cefotaxime (Hoberman 1999) or ceftriaxone (Bocquet 2012; Montini 2007; Neuhaus 2008) for three to four days or until resolution of fever followed by oral antibiotics to complete the course of therapy.

- Time to resolution of fever did not differ significantly between groups (Analysis 1.1 (2 studies, 808 children): MD 2.05 hours, 95% CI -0.84 to 4.94; I^2 = 0%). Neuhaus 2008 reported the number of children with fever on day three did not differ significantly between groups (Analysis 1.2 (1 study, 152 children): RR 0.79, 95% CI 0.30 to 2.06).
- The number of children with persistent UTI at 72 hours after commencing therapy did not differ significantly between groups (Analysis 1.3 (2 studies, 542 children): RR 1.10, 95% CI 0.07 to 17.41).
- Montini 2007 reported no significant difference between groups in the mean levels of inflammatory markers: WCC (Analysis 1.4.1 (1 study, 473 children): MD 0.30 x 10^9/L, 95% CI -0.30 to 0.90), ESR (Analysis 1.4.2 (1 study, 338 children): MD -1.80 mm/60 min, 95% CI-8.20 to 4.60]) or CRP (Analysis 1.4 (1 study, 486 children): MD 1.10 mg/L, 95% CI -2.18 to 4.38).
- Hoberman 1999 reported no significant difference between groups in the rate of recurrences of bacteriuria (Analysis 1.5.1 (1 study, 287 children): RR 0.65, 95% CI 0.28 to 1.51) or symptomatic UTI within six months (Analysis 1.5.2 (1 study, 287 children): RR 0.67, 95% CI 0.27 to 1.67).
- There were no significant differences among treatment groups in the rate of persistent kidney parenchymal defects on DMSA scan whether considered in relation to the total number of children with acute pyelonephritis (Analysis 1.6.1 (4 studies, 943 children): RR 0.82, 95% CI 0.59 to 1.12; I^2 = 41%) or only those with defects on the initial DMSA scan (Analysis 1.6.2 (4 studies, 681 children): RR 0.79, 95% CI 0.31 to 1.03; I^2 = 19%). Hoberman 1999 reported no significant difference between groups in the size of persistent kidney parenchymal defects on DMSA scan (Analysis 1.7 (1 study, 272 children): MD -0.70, 95% CI -1.74 to 0.34).
- Post hoc subgroup analysis (Analysis 1.8) by Hoberman 1999 found no difference in the number of kidney parenchymal defects on DMSA scan at six months between children with VUR (Analysis 1.8.1 (1 study, 107 children): RR 1.88, 95% CI

0.83 to 4.24) and those without VUR (Analysis 1.8.2 (1 study, 107 children): RR 0.80, 95% CI 0.23 to 2.73). However, post hoc analysis (Analysis 1.8.4) raised the possibility that among children with VUR (grades III-V), persistent kidney parenchymal defects on DMSA scan at six months occurred more frequently after oral than IV therapy (RR 7.33, 95% CI 1.00 to 54.01).

- The average cost of treatment for each patient was USD 3630 and USD 7382 for oral and IV groups respectively (Hoberman 1999).
- Adverse effects were reported in three studies (Bocquet 2012; Montini 2007; Neuhaus 2008). No children experienced therapy-related adverse effects in Neuhaus 2008. In Bocquet 2012 two children experienced vomiting with oral cefixime and required change to parenteral therapy. In Montini 2007 15 children experienced diarrhoea or vomiting (13), erythema (1) and leucopenia (1) with oral amoxicillin and clavulanic acid; 10 required a change of antibiotics. In the same study three children experienced diarrhoea (1), erythema (1) and candida (1) with ceftriaxone; none required change of treatment. Hoberman 1999 did not report on adverse effects.

Sequential short duration (three to four days) IV therapy and oral therapy versus long duration (seven to 14 days) IV therapy

There were six studies (Benador 2001; Bouissou 2008; Francois 1997; Levtchenko 2001; Noorbakhsh 2004; Vilaichone 2001) involving 917 children that compared oral therapy after an initial three to four days of IV therapy with a long duration of IV therapy alone. Two studies compared IV ceftriaxone (three to four days) followed by oral cefixime (Benador 2001) or ceftibuten (Vilaichone 2001) with IV ceftriaxone (10 days). Levtchenko 2001 compared IV temocillin (three days) followed by oral amoxicillin or amoxicillin/clavulanic acid with IV temocillin (seven days). Noorbakhsh 2004 compared IV ceftriaxone (two to three days) followed by oral ceftibuten with IV amikacin or gentamicin with IV ampicillin (14 days). Francois 1997 compared IV cefotaxime (four days) followed by oral amoxicillin/clavulanic acid with IV cefotaxime (14 days). Bouissou 2008 compared IV netilmicin (two days) and ceftriaxone (three days) followed by oral antibiotics (cefixime, amoxicillin/clavulanic acid, TMP/SMX) chosen according to sensitivity with IV netilmicin (two days) and ceftriaxone (eight days). Benador 2001 and Levtchenko 2001 also converted the IV group to oral therapy after seven to 10 days to complete 15 to 21 days of treatment.

- There was no significant difference between the risk of persistent bacteriuria at the end of treatment (Analysis 2.1 (4 studies, 305 children): RR 0.78, 95% CI 0.24 to 2.55; I^2 = 0%).
- There was no significant difference between groups for recurrent UTI within six months (Analysis 2.2 (5 studies, 993 children): RR 0.97, 95% CI 0.58 to 1.62; I^2 = 0%).
- The number of persisting kidney parenchymal defects seen on DMSA scan at three to six months did not differ significantly between treatment groups when considered in relation to the total number of children with acute pyelonephritis (Analysis 2.3.1 (4 studies, 726 children): RR 1.01, 95% CI 0.80 to 1.29; I^2 = 0%) or only those with defects on the initial DMSA scan (Analysis 2.3.2 (3 studies, 315 children): RR 1.10, 95% CI 0.84 to 1.45; I^2 = 0%).
- Post hoc subgroup analysis showed that the number of children with persisting kidney parenchymal defects on DMSA scan did not differ between those with VUR (Analysis 2.4.1 (2 studies, 81 children): RR 0.99, 95% CI 0.69 to 1.43; I^2 = 0%) and without VUR (Analysis 2.4.2 (2 studies, 173 children): RR 1.19, 95% CI 0.81 to 1.76; I^2 = 0%), those aged under one year (Analysis 2.4.3 (1 study, 22 children): RR 1.46, 95% CI 0.71 to 3.01) and aged one year and over (Analysis 2.4.4 (1 study, 54 children): RR 0.89, 95% CI 0.59 to 1.34), and those who had a delay of treatment of less than seven days (Analysis 2.4.5 (1 study, 13 children): RR 1.52, 95% CI 0.59 to 3.92) or more than seven days (Analysis 2.4.6 (1 study, 8 children): RR 2.10, 95% CI 0.92 to 4.77).
- Adverse effects were reported in Francois 1997 and Vilaichone 2001; both related to gastrointestinal upsets, and frequency did not differ between therapy routes (Analysis 2.5.1 (2 studies, 175 children): RR 1.29, 95% CI 0.55 to 3.05; I^2 = 0%). Four studies did not report on adverse effects (Benador 2001; Bouissou 2008; Levtchenko 2001; Noorbakhsh 2004).
- Duration of hospitalisation was 4.9 days for the IV and oral group compared with 9.8 days for the IV group (Vilaichone 2001).
- Costs of treatment for four days of IV therapy followed by six days of oral therapy were 513 French Francs (range 176 to 896) compared with 3545 French Francs (range 2478 to 4673) for 10 days of IV therapy (Francois 1997).

Single dose parenteral therapy and oral treatment versus oral therapy alone

Baker 2001 (69 children) compared the addition of a single intramuscular dose of the third generation cephalosporin, ceftriaxone, to an oral course of TMP/SMX. There was no significant difference in:

- persistence of bacteriuria after 48 hours (Analysis 3.1: RR 0.77, 95% CI 0.19 to 3.20)
- persistence of clinical symptoms (Analysis 3.2: RR 0.82, 95% CI 0.24 to 2.81), or
- total adverse events (Analysis 3.4.1: RR 1.37, 95% CI 0.33 to 5.68) between groups.

No child developed symptomatic UTI during one month after treatment.

Different dosing regimens of aminoglycoside therapy

Three studies that involved 495 children compared daily parenteral administration of gentamicin (Carapetis 2001; Chong 2003) or netilmicin (Vigano 1992) to eight-hourly administration of aminoglycosides.

- There was no significant difference in the risk for persisting bacteriuria one to three days after commencing treatment with either dose frequency (Analysis 4.1 (3 studies, 435 children): RR 1.05, 95% CI 0.15 to 7.27).
- Carapetis 2001 reported no difference in numbers of children with persisting clinical symptoms after three days of gentamicin (Analysis 4.2 (1 study, 179 children): RR 1.98, 95% CI 0.37 to 10.53).
- Vigano 1992 reported persisting bacteriuria one week after (Analysis 4.3 (1 study, 144 children): RR 2.84, 95% CI 0.12 to 68.57) and recurrent UTI within one month (Analysis 4.4 (1 study, 144 children): RR 1.18, 95% CI 0.33 to 4.23) after completing netilmicin treatment did not differ between treatment groups.
- There was no significant difference in numbers of children with hearing impairment (Analysis 4.5 (3 studies, 271 children): RR 2.83, 95% CI 0.33 to 24.56; I^2 = 0%) or kidney dysfunction

(Analysis 4.6 (3 studies, 419 children): RR 0.75, 95% CI 0.20 to 2.82; I^2 = 0%).

- Chong 2003 reported mean time to resolution of fever with gentamicin did not differ between groups (Analysis 4.7 (1 study, 172 children): MD 2.40 hours, 95% CI -7.90 to 12.70). Median time to resolution of fever was 27 hours (interquartile range 15 to 48 hours) with daily dosing and 33 hours (interquartile range 12 to 48 hours) with eight-hourly dosing in a second study (Carapetis 2001).

Different antibiotic agents

Six studies compared different antibiotics (Bakkaloglu 1996; Carapetis 2001; Chong 2003; Kafetzis 2000; Schaad 1998; Vigano 1992).

Third generation cephalosporins versus other antibiotics

In four studies involving 491 children treatment with third generation cephalosporins (IV cefotaxime (Fischbach 1989), oral cefetamet (Toporovski 1992) or oral ceftibuten (Banfi 1993; Marild 2009) were compared with amoxicillin/clavulanic acid (Fischbach 1989; Toporovski 1992) or TMP/SMX (Banfi 1993; Marild 2009).

- There was no significant difference in the number of children with persistent bacteriuria after 48 hours of therapy (Analysis 5.1 (3 studies, 433 children): RR 2.41, 95% CI 0.98 to 5.93; I^2 = 0%).
- There was no significant difference in numbers of children who had recurrent UTI at 4 to 10 days after treatment (Analysis 5.2 (4 studies, 419 children): RR 1.23, 95% CI 0.32 to 4.74; I^2 = 0%).
- A significantly greater number of children treated with TMP/SMX had persistent clinical symptoms at four to 10 days after treatment compared with those treated with a third generation cephalosporin (Analysis 5.3 (3 studies, 471 children): RR 0.28, 95% CI 0.13 to 0.62; I^2 = 0%). The study by Marild 2009 contributed to 94% of the weight of this result.
- Fischbach 1989 reported no significant difference in numbers of children with persistent fever for more than 48 hours (Analysis 5.4 (1 study, 20 children): RR 5.00, 95% CI 0.27 to 92.62).
- Banfi 1993 reported no significant difference between groups in the rate of recurrences of bacteriuria (Analysis 5.5 (1 study, 28 children): RR 2.14, 95% CI 0.11 to 40.30) or symptomatic UTI at four to six weeks (Analysis 5.6; no symptomatic UTIs in either group).
- All four studies reported adverse effects. There was no significant difference in numbers of children who experienced gastrointestinal adverse effects (Analysis 5.7 (4 studies, 591 children): RR 0.93, 95% CI 0.34 to 2.58; I^2 = 0%). Marild 2009 reported that four children in each group discontinued treatment because of adverse reactions (Analysis 5.8 (1 study, 461 children): RR 0.49, 95% CI 0.12 to 1.94).

Third generation cephalosporins versus fourth generation cephalosporins (Analysis 6)

In Schaad 1998, which included 299 children, IV cefepime (a fourth generation cephalosporin) was compared to IV ceftazidime (a third generation cephalosporin).

- No significant differences between groups were detected in numbers of children with persistent or recurrent bacteriuria with the same pathogen at different time points after therapy (Analysis 6.1).
- Recurrent UTI with a different pathogenic organism at four to six weeks did not differ between groups (Analysis 6.2: RR 1.19, 95% CI 0.45 to 3.18).
- There were no significant differences in the occurrence of an unsatisfactory clinical response at different time points after therapy (Analysis 6.3).
- The frequency of adverse effects did not differ between treatment groups (Analysis 6.4).

Ceftriaxone versus cefotaxime

Bakkaloglu 1996 compared ceftriaxone and cefotaxime in 100 children aged over 24 months.

- No child had persistent bacteriuria at 48 hours (Analysis 7.1).
- There were no significant differences between groups for bacteriuria at the end of treatment (Analysis 7.2.1: RR 0.87, 95% CI 0.37 to 2.03), for recurrent infection at one month after therapy (Analysis 7.3.1: RR 0.68, 95% CI 0.30 to 1.50), or for total adverse events (Analysis 7.4.1: RR 0.67, 95% CI 0.12 to 3.82).
- Post hoc subgroup analysis (Analysis 7.2.2 and Analysis 7.2.3) revealed no differences in outcomes for bacteriuria at the end of treatment or recurrent UTI at one month after therapy between children with and without abnormalities on imaging studies of the urinary tract.

Aminoglycosides

Kafetzis 2000 compared the aminoglycosides isepamicin and amikacin in 16 children.

- No child in either group had persistent bacteriuria after 48 hours of treatment, or seven days or 30 days after treatment (Analysis 8.1).
- Mean time to resolution of fever in each group was identical (24 hours).
- No child in either treatment group developed hearing impairment on testing.

Duration of antibiotic administration

Four studies compared different durations of antibiotic administration (Cheng 2006; Grimwood 1988; Pylkkänen 1981; Repetto 1984).

Ten days versus 42 days of oral sulphafurazole

The study by Pylkkänen 1981 involved 149 children and compared 10 days with 42 days of oral sulphafurazole.

- Recurrence of UTI within one month of ceasing therapy was significantly higher in children treated for 10 days compared with children treated for 42 days (Analysis 9.1: RR 17.70, 95% CI 2.42 to 129.61).
- The number of children with recurrent UTI from one to 12 months after ceasing therapy did not differ between groups (Analysis 9.2: RR 0.87, 95% CI 0.40 to 1.88).

Single dose parenteral antibiotic therapy versus seven to 10 days of oral therapy

Grimwood 1988 and Repetto 1984 (involving a total of 61 children) compared single dose parenteral antibiotic therapy with seven to 10 days of oral therapy.

- There were no significant differences in the number of children with persistent bacteriuria after treatment (Analysis 10.1 (2 studies, 35 children): RR 1.73, 95% CI 0.18 to 16.30; I^2 = 15%) or with recurrent UTI within six weeks (Analysis 10.2 (2 studies, 35 children): RR 0.24, 95% CI 0.03 to 1.97).

Three weeks with two weeks of antibiotics

Cheng 2006, which involved 80 children, compared three weeks with two weeks of antibiotics for children with acute lobar nephronia. Antibiotics were chosen according to sensitivities.

- Seven children treated for two weeks had persistent or recurrent bacteriuria; this was not significantly different (Analysis 11.1: RR 0.07, 95% CI 0.00 to 1.19).
- Two children had recurrence of clinical symptoms with bacteriuria; this was not significantly different (Analysis 11.2: RR 0.21, 95% CI 0.01 to 4.24).

Three days with 10 days of antibiotics

Khan 1981 (54 children) compared three and 10 days of oral antibiotics. Data were reported as episodes of UTI (asymptomatic, lower tract, APN) and could not be included in a meta-analysis. Of 31 episodes of UTI, 23 were cured in 27 children in the three day treatment group and 25 of 31 episodes were cured in 27 children in the 10 day treatment group. Of episodes of acute pyelonephritis, four were cured in five episodes in the three day treatment group and five were cured in six episodes in the 10 day treatment group.

Different routes of antibiotic administration

Fujii 1987, which reported on 105 children, compared ampicillin administered by suppository with oral administration.

- There was no significant difference between treatments in the risk of persistent clinical symptoms (Analysis 12.1: RR 0.89, 95% CI 0.51 to 1.56) or bacteriuria (Analysis 12.2: RR 0.89, 95% CI 0.53 to 1.50).

DISCUSSION

Summary of main results

This review was designed to include all RCTs addressing all aspects of antibiotic treatment for children with acute pyelonephritis. Identified studies formed a heterogeneous group with few studies addressing the same or similar comparisons to enable assessment in meta-analyses. The 27 included studies addressed a variety of different questions related to the therapy of children with acute pyelonephritis.

Oral therapy versus IV therapy

Four studies compared an oral antibiotic (ceftibuten, cefixime or amoxicillin/clavulanic acid) alone with IV therapy (cefotaxime or ceftriaxone) followed by oral therapy. These studies found:

- No significant difference in bacteriological outcomes between groups.
- The number of children with kidney parenchymal damage on DMSA scan at follow-up whether expressed as a proportion of the total number considered to have acute pyelonephritis or as a proportion of those with DMSA changes at entry did not differ significantly between groups.

Thus, there were no significant differences in efficacy between treatment with oral ceftibuten, cefixime and amoxicillin/clavulanic acid and IV therapy followed by oral therapy. Studies that support these findings enrolled children older than one month of age and hence the finding cannot be extrapolated to children aged less than one month.

Short duration versus long duration IV therapy

A meta-analysis of six studies showed:

- No significant differences in clinical or bacteriological outcomes between IV antibiotic therapy given for three to four days followed by oral therapy and IV therapy for seven to 14 days.
- That the prevalence of kidney parenchymal injury on DMSA scan at three to six months after UTI therapy did not differ significantly between treatment groups.

These data show that short duration IV therapy (three to four days) can be used instead of longer courses of IV therapy to treat childhood acute pyelonephritis. The findings cannot be extrapolated to children less than one month of age as such children were excluded from the studies.

Single daily dosing with aminoglycosides

If IV therapy is required, three studies provide data to support the safety and efficacy of daily dosing with aminoglycosides (gentamicin and netilmicin) compared with eight-hourly dosing in children with acute pyelonephritis. Once daily dosing has been studied extensively in adults and is preferred due to improved efficacy, similar or reduced toxicity, convenience and lower costs. These findings have also been supported in children justifying the use of single daily dosing of aminoglycosides (Contopoulos-Ioannidis 2004; Jenh 2011), although aminoglycoside pharmacokinetics and toxicity differ in children from adults.

Efficacy of different antibiotics

The seven studies that compared different antibiotics did not demonstrate any advantage of one agent over another. Four studies compared a cephalosporin with amoxicillin/clavulanic acid or TMP/SMX. A meta-analysis of three studies demonstrated that children treated with oral ceftibuten had a higher clinical cure rate than TMP/SMX. However one large study (Marild 2009) contributed most of the weight of the analysis. The study defined clinical cure as the resolution of all symptoms related to the infection within 10 days. It is possible that there was some cross-over of symptoms related to the infection and those due to adverse effects of medication such as vomiting. Furthermore, the study did not demonstrate any difference in bacteriological elimination rates despite 15% of the pathogens responsible for the infection being resistant to TMP/SMX compared to 2% that were resistant to ceftibuten.

One study demonstrated that a single dose of parenteral medication added to oral therapy did not improve efficacy compared with oral therapy alone.

Adverse events

Adverse events resulting from antibiotics were reported in 16 studies. Events were uncommon and rarely resulted in treatment discontinuation or significant alteration.

Overall completeness and applicability of evidence

In this review a comprehensive and extensive literature review was performed to identify studies that assessed the benefits and harms of antibiotics to treat children with acute pyelonephritis. We found that oral antibiotic therapy alone is as effective as IV therapy followed by oral therapy, and similarly short IV therapy is as effective as longer courses of IV therapy to treat childhood acute pyelonephritis. It is unknown whether these findings apply to children less than one month of age since children aged below one month of age were excluded from studies. The exclusion criteria for participation in the included studies mean that our findings may not be generalizable to all children with acute pyelonephritis. There were 10 studies that excluded children who were severely ill or clinically unstable. Four studies did not specify any exclusion criteria. The applicability of the findings in children with uropathy may also be limited since 10 studies excluded children with known uropathy. Hoberman 1999 performed a post hoc subgroup analysis to analyse differences in efficacy between children with or without VUR but the study was not designed and had no power to detect differences between small subgroups. Further data are required to determine whether treatment efficacy differs in children with non-dilating VUR (grades I-II) and dilating VUR (grades III-V).

Most of the studies examined the bacteriological efficacy of antibiotic therapy. Few studies compared the efficacy of antibiotic therapies on the resolution of clinical symptoms other than fever.

None of the 27 included studies analysed the optimal duration of antibiotic therapy for childhood acute pyelonephritis. Our review evaluated oral antibiotic regimens in which oral antibiotics were used either alone or following IV antibiotics for a total duration of eight to 42 days of therapy. Inadequate data are available on the benefits and harms of shorter duration therapies (e.g. seven days or less). Three studies compared single dose parenteral antibiotic therapy or short course oral therapy with seven to 10 days of oral therapy and showed no significant differences but the studies were small. This is unlike the evidence supporting the use of short-course therapies for the treatment of lower urinary tract infections in children (Michael 2002; Michael 2003).

From the low reported incidence of adverse events, we were only able to detect common adverse effects e.g. gastrointestinal upsets. Generally, RCTs are not powered to detect rare but serious side effects e.g. Stevens–Johnson syndrome, so our findings of adverse effects may not be generalizable to larger groups of children.

Most of the included studies reported on short-term outcomes. Nine studies analysed kidney parenchymal damage on DSMA scan at three to 12 months following an episode of acute pyelonephritis. Five of the nine studies had a high loss to follow up because of refusal to do a DMSA scan among well children and one study (not included) was terminated without any results for this reason (NCT00724256). The loss to follow up of well children may lead to an underestimate of the effect of treatment. As the longest follow up of children was 12 months, this review cannot provide data on the likelihood of long term kidney scarring following antibiotic therapy.

Although several studies potentially included adolescents aged to 16 years, none of the studies reported results for different age groups. Thus we could not determine whether there was any difference in results according to the patients' ages.

Quality of the evidence

The quality of the included studies was quite variable. The main limitations in the quality of the studies were concealment of allocation, blinding of participants and personnel and sponsorship from pharmaceutical companies. Of the 27 included studies, 12 reported adequate sequence generation and six demonstrated adequate allocation concealment. The lack of adequate sequence generation and allocation concealment can lead to biased estimates of treatment effects in the original study and therefore the results of a systematic review (Hollis 1999; Juni 1999; Moher 1998; Schulz 1995). All of the studies were unblinded to participants and personnel primarily because antibiotics were delivered by the parenteral route compared with oral or used different dosing regimens. This was considered a high risk of bias because clinicians' management could be influenced by knowledge of the treatment group. For blinding of outcome assessors, blinding was adequate in 17 studies where the primary outcome was bacteriological or radiological and considered unlikely to be influenced by lack of blinding. We found that 19 studies provided complete data reporting and 13 reported on all reasonably expected outcomes (bacteriological eradication, clinical cure and adverse effects). The authors of 11 studies reported receiving sponsorship from pharmaceutical companies.

The quality of the evidence was assessed according to the GRADE approach and is displayed in summary of findings tables.

The evidence that oral therapy alone is as effective as IV therapy followed by oral therapy in children with acute pyelonephritis is considered to be of moderate quality. The quality of evidence was downgraded because of imprecision regarding the time to resolution of fever and the loss to follow-up for DMSA scans (Summary of findings for the main comparison).

The evidence that short duration IV therapy followed by oral therapy is as effective as long duration IV therapy is considered to be of moderate quality. The quality of evidence was downgraded because of unclear or inadequate allocation concealment in the included studies which may increase the risk of selection bias, the studies being too small and the loss to follow-up for DMSA scans (Summary of findings 2).

The evidence that daily dosing of aminoglycosides is as safe and effective as thrice daily dosing of aminoglycosides is considered to be of low quality. The quality of evidence was downgraded because of unclear allocation concealment in two of three studies and the small number of participants combined with the low frequency of events that made the analysis significantly underpowered to detect a difference (Summary of findings 3).

The evidence that third generation cephalosporins are no more effective than other antibiotics (amoxicillin/clavulanic acid and TMP/SMX) is low. The quality of evidence was downgraded because of unclear allocation, imprecision from sparse data, and inconsistent bacteriologic results from one study that provided most of the weight of the meta-analysis (Summary of findings 4).

Potential biases in the review process

We attempted to reduce publication bias by searching multiple databases and the grey literature without language restriction. Although the Cochrane Renal Group's Specialised Register contains the handsearched reports of studies, it is possible that we

missed unpublished data presented at smaller conferences or studies published in foreign language journals and low impact journals. Studies may have been added since our last search of the register. No data were available from the terminated study (NCT00724256) after personal communication with the lead author. Not all included studies reported all outcomes. Some outcomes that would be expected to be known (e.g. resolution of clinical symptoms) were not reported which may have affected the results of meta-analyses.

Agreements and disagreements with other studies or reviews

A systematic review published in 2008 evaluated an early switch to oral antibiotics after at least one day of initial IV antibiotics with IV therapy alone for hospitalised patients with acute pyelonephritis (Vouloumanou 2008). The meta-analysis included both children and adults with acute pyelonephritis but the data from the two populations could be separated. It identified all six RCTs in children that we included in our review for this comparison. The authors found there was no difference in the incidence of kidney scars, microbiological eradication, clinical cure, reinfection, persistence of acute pyelonephritis, or adverse events between the two treatment regimens. This is consistent with our finding that short duration IV therapy followed by oral therapy is as effective as longer courses of IV therapy for the treatment of acute pyelonephritis in children.

No other systematic reviews were found for the 11 other comparisons in our review.

This review agrees with recently published guidelines (AAP 2011; Ammenti 2012; NICE 2007) for the treatment of childhood UTI, which recommend oral antibiotics for the initial treatment of children with acute pyelonephritis unless the child is seriously ill and/or unable to tolerate oral antibiotics. Our findings can be applied to children aged over one month. The NICE 2007 guidelines apply to children aged three months or older, the AAP 2011 guidelines apply to children aged 2 to 24 months and the Ammenti 2012 recommendations apply to children aged two months to three years. The guidelines also suggest seven or more days of antibiotic treatment but recognise that this is not based on best evidence because there are no data on the optimal duration of antibiotic therapy, particularly shorter courses.

AUTHORS' CONCLUSIONS

Implications for practice

The following implications for practice in the treatment of children with acute pyelonephritis have been identified:

- Oral antibiotics (cefixime, ceftibuten or amoxicillin/clavulanic acid) given alone for 10 to 14 days are as effective as sequential IV therapy given for three days followed by oral therapy for a total duration of 10 to 14 days suggesting that children with acute pyelonephritis can be treated effectively with oral antibiotics.
- If IV antibiotic therapy is given, a short course of IV therapy given for two to four days followed by oral therapy with total therapy duration of 10 to 21 days is as effective as a longer duration of IV antibiotic therapy given for seven to 10 days with total duration of therapy of 10 to 21 days.
- Studies comparing oral therapy alone with IV then oral antibiotics or IV then oral with IV therapy involved children greater than one month of age and were biased towards children who were less sick and so findings cannot be extrapolated to children less than one month of age or who are severely ill. The studies were also not stratified according to the grade of VUR so it remains unclear whether results differ according to the presence or absence of dilating VUR (grades III-V).
- Adequate data from RCTs are not available to determine the optimal total duration of antibiotic therapy required for acute pyelonephritis.

Implications for research

Further RCTs are required to determine the benefits and harms in children of different ages with acute pyelonephritis of:

- Treatment for shorter periods (seven days or less) compared with 10 to 14 days.
- Initial treatment with oral antibiotics compared with parenteral therapy or IV then oral therapy compared with IV therapy in children with dilating VUR or other major urinary tract malformation.
- Treatment with aminoglycosides alone or in combination with other antibiotics compared with other antibiotics including third generation cephalosporins in initial parenteral treatment.
- Treatment with cheaper and more widely available oral antibiotics e.g. cephalexin.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Baker 2001

Methods	• Study design: parallel RCT • Study duration: 1 September 1996 to 31 March 1998 • Duration of follow-up: 1 month
Participants	• Country: USA • Setting: tertiary hospital ED

Baker 2001 *(Continued)*

- Children 6 months to 12 years; temperature > 38°C and diagnosed as having a UTI based on presenting history, physical examination and urinalysis findings
- Urine collection: MSU or catheter
- Number: treatment group 1 (34); treatment group 2 (35)
- Mean age (years): treatment group 1 (3.6); treatment group 2 (3.8)
- Sex (M/F): treatment group 1 (5/30); treatment group 2 (2/34)
- Exclusion criteria: patients with known uropathy; current antibiotic therapy; allergy to study antibiotics; clinically unstable patients

Interventions	Treatment group 1 • IM ceftriaxone: 50 mg/kg, single dose • Oral TMP/SMX: 5 mg/kg/d twice daily for 10 days Treatment group 2 • Oral TMP/SMX: 5 mg/kg/d twice daily for 10 days
Outcomes	• Urine culture at 48 hours • Admission at 48 hours • UTI and/or admission at 1 month • Adverse effects
Notes	• Definition of APN: UTI and fever > 38°C • 87 enrolled; 18 excluded (no growth on urine 14, no FU 4); 69 included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The patient's nurse blindly selected opaque envelopes containing group assignment from a bin"
Allocation concealment (selection bias)	Low risk	"The patient's nurse blindly selected opaque envelopes containing group assignment from a bin"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo injections so participants aware of assignment. "Physicians caring for the patients were unaware of study group assignment".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinicians caring for the children were unaware of the assignment at follow up. "Physician caring for patient at follow-up usually was not the physician who cared for the patient at first visit". All children had bandage on thigh (IM injection)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four (5.5%) lost to FU and excluded. Unlikely to influence results as balanced across groups.
Selective reporting (reporting bias)	Low risk	Reported all expected outcomes
Other bias	High risk	Study grant from Roche Pharmaceuticals, Denver, Colorado

Bakkaloglu 1996

Methods	• Study design: RCT • Study duration: NS • Duration of follow-up: 1 month
Participants	• Country: Turkey • Setting: tertiary IP • Children ≥ 2 years • Urine collection: NS • Number: treatment group 1 (50); treatment group 2 (50) • Mean age ± SD (years): treatment group 1 (8.1 ± 3.6); treatment group 2 (8.3 ± 2.9) • Sex (M/F): treatment group 1 (12/38); treatment group 2 (10/40) • Uropathy: treatment group 1 (24); treatment group 2 (21) • Exclusion criteria: NS
Interventions	Treatment group 1 • IV ceftriaxone: 50 mg/kg daily for 10 days Treatment group 2 • IV cefotaxime: 50 mg/kg twice daily for 10 days
Outcomes	• Persistent bacteriuria at 2 to 3 days • Persistent bacteriuria at 10 days • Recurrent UTI within 4 to 5 weeks • Adverse events
Notes	• Definition of APN: UTI and 2+ of fever, flank pain, pyuria, bacteriuria.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Said to be "double-blind, randomized clinical trial" but no placebo injection given to ceftriaxone group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Lack of blinding could influence assessment of clinical response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in follow-up
Selective reporting (reporting bias)	Low risk	Reports expected outcomes (clinical and bacteriological response, adverse effects)
Other bias	High risk	Grant from Hoffmann La Roche Ltd

Banfi 1993

Methods	• Study design: parallel RCT • Study duration: 31 August 1989 to 16 November 1990 • Duration of follow-up: 4 to 6 weeks

Participants	• Country: South America/Europe
	• Setting: multicentre; IP/OP
	• Symptomatic UTI including children with uncomplicated, complicated and upper UTI; aged: ≥ 12 years
	• Urine collection: clean catch, catheter, suprapubic
	• Number
	  * Safety population/APN: treatment group 1 (154/52); treatment group 2 (74/21)
	  * Efficacy population/APN: treatment group 1 (101/36); treatment group 2 (50/15)
	• Mean age, range (years)
	  * Safety population: treatment group 1 (5.5, 0.25 to 12); treatment group 2 (5.1, 0.5 to 12)
	  * Efficacy population: treatment group 1 (6.4, 0.5 to 12); treatment group 2 (6.0, 0.5 to 12)
	• Sex (M/F)
	  * Safety population: treatment group 1 (35/119); treatment group 2 (18/56)
	  * Efficacy population: treatment group 1 (17/84); treatment group 2 (7/43)
	• Uropathy: treatment group 1 (28); treatment group 2 (9)
	• 52 APN included in safety; 36 in efficacy
	• Exclusion criteria: Cystitis episodes < 3/year; persistent UTI with uropathy; infections likely to need treatments other than study drugs; antibiotics within last 2 weeks; other study drug in < 4 weeks; other serious illness; pregnant, nursing or not using contraceptives; kidney abscess; history of hypersensitivity.

Interventions	Treatment group 1 • Oral ceftibuten: 9 mg/kg/d (max 400 mg/d) for 10 days Treatment group 2 • Oral TMP/SMX: 8 mg/40 mg/kg/d (max 320/1600) for 10 days
Outcomes	• Bacterial response at 5 to 9 days and 4 to 6 weeks after treatment completed • Clinical response at 5 to 9 days and 4 to 6 weeks after treatment completed • Adverse effects • Time to resolution of symptoms
Notes	• Definition of APN not provided • 3/231 (1.3%) excluded from safety analysis. 80/231 (34.6%) excluded from efficacy (did not meet entry criteria (51); mis-randomisation (6); efficacy data not available (18); other (5))

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be randomly assigned. 2:1 ratio
Allocation concealment (selection bias)	Unclear risk	Said to be randomly assigned
Blinding of participants and personnel (performance bias)	High risk	No blinding and lack of blinding could influence clinical management

Banfi 1993 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding and lack of blinding could influence clinical outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	16% of total group excluded from analysis for reasons other than not meeting entry criteria and this could influence results
Selective reporting (reporting bias)	Low risk	Data reported on clinical & bacteriologic response & adverse effects
Other bias	Unclear risk	No information provided

Benador 2001

Methods	• Study design: parallel RCT • Study duration: June 1995 to April 1999 • Duration of follow-up: 3 months • Power analysis: 106/group to detect difference in rate of kidney scarring of 20%.
Participants	• Country: Switzerland • Setting: multicentre (2), tertiary hospitals, IP • Children aged 3 months to 16 years with probable APN • Urine samples: bag, MSU, SPA • Number: treatment group 1 (111); treatment group 2 (118) • Median age, IQR (years): treatment group 1 (2.4, 0.8 to 5.6); treatment group 2 (1.0, 0.5 to 3.3) • Sex (M/F): treatment group 1 (22/89); treatment group 2 (88/30) • Uropathy/VUR: treatment group 1 (42/36); treatment group 2 (44/40) • Exclusion criteria: allergy to cephalosporins; known uropathology
Interventions	Treatment group 1 • IV ceftriaxone: 50 mg/kg daily for 3 days • Oral cefixime: 4 mg/kg/dose, 2 doses/d for 12 days (days 4 to 15) • Total 15 days Treatment group 2 • IV ceftriaxone: 50 mg/kg daily for 10 days • Oral cefixime: 4 mg/kg/dose, 2 doses/d for 5 days (days 11 to 15) • Total 15 days
Outcomes	• Scarring on DMSA at 3 months • Recurrent UTI at 3 months
Notes	• Definition of APN: UTI and acute focal lesions on DMSA in patients with fever > 38°C, flank pain, constitutional symptoms, CRP > 10 mg/L • 206/435 randomised were excluded as they had negative urine culture (84) or no acute pyelonephritis changes on first DMSA (122)
Risk of bias	

Benador 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocks of 20 sealed opaque envelopes with equal numbers of treatment assignments, stratified by centre
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome (DMSA scans) assessed by radiologists unaware of patient assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	9 (8 in 10 day group, 1 in 3 day group) of 229 (4.4%) were excluded from results. Unlikely to influence results
Selective reporting (reporting bias)	Low risk	Reported expected outcomes + DMSA outcome
Other bias	Unclear risk	No information provided

Bocquet 2012

Methods	• Study design: parallel RCT • Study duration: August 2004 to April 2008 (recruitment) • Duration of follow-up: 6 to 8 months • Power analysis: 349/group to detect difference in rate of kidney scarring of 20%

Participants	• Country: France
	• Setting: multicentre (10); hospital ED
	• Children aged 1 month to 36 months; first febrile UTI; temperature ≥ 38.5°C; positive urine for WBC and gram negative rods; pro-calcitonin ≥ 0.5 ng/mL; normal kidney ultrasound & pre-natal ultrasound; no known uropathy
	• Urine samples: bag, MSU, SPA
	• Number: treatment group 1 (85); treatment group 2 (86)
	• Mean age ± SD (years): treatment group 1 (8.9 ± 6); treatment group 2 (10.6 ± 7.6)
	• Sex (M/F): treatment group 1 (34/51); treatment group 2 (25/61)
	• Uropathy (VUR): treatment group 1 (18); treatment group 2 (22)
	• Exclusion criteria
	  * Primary: allergy to study medications; severely ill children; vomiting and/or diarrhoea precluding oral medication; uncertain adherence; received antibiotic therapy in 5 days before inclusion
	  * Secondary: normal DMSA; procalcitonin < 0.5 ng/mL, urine culture negative or > 1 organism or resistant to study drugs; recurrence of APN before 2nd DMSA

Interventions	Treatment group 1 • Oral cefixime: 8 mg/kg single dose, then oral 4 mg/kg/dose twice daily for 10 days Treatment group 2

Bocquet 2012 *(Continued)*

	• IV ceftriaxone: 50 mg/kg daily for 4 days • Oral cefixime: 4 mg/kg/dose twice daily for 6 days (days 5 to 10)
Outcomes	• Scarring on DMSA at 6 months • Resolution of fever • Adverse effects
Notes	• Definition of APN: UTI and acute focal lesions on DMSA in patients with fever > 38.5°C, procalcitonin ≥ 0.05 ng/mL • ITT population included in analysis • 52/171 (30%) excluded for no APN on DMSA (25), no DMSA (2), protocol violation (5), withdrawal of consent (8), problems with obtaining results of MSU (10) or procalcitonin (2)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated code (Clean Web)". Blocked and stratified by centre and age (≤ 1 year/> 1 year)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Clinical management could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome (DMSA scans) assessed without knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	18.5% (27/146) excluded for reasons other than no APN on acute DMSA
Selective reporting (reporting bias)	High risk	No report on bacteriologic resolution of UTI
Other bias	Low risk	Ministry of Health via Unit of Clinical Research, Necker Hospital, grant PHRC no. AOM 04 105

Bouissou 2008

Methods	• Study design: parallel RCT • Study duration: January 1999 to June 2003 • Duration of follow-up: 6 to 9 months • Power analysis: 493 participants to detect difference in rate of kidney scarring of 10%
Participants	• Country: France • Setting: multicentre (17) hospital IP • Children aged 3 months to 16 years; temperature > 38°C; positive urine for nitrite, WBC, bacteriuria > 10^5/mL, CRP > 20 mg/L; no known uropathy • Urine samples: bag, MSU, SPA

Bouissou 2008 *(Continued)*

- Number (randomised/analysed): treatment group 1 (277/205); treatment group 2 (271/178)
- Mean age, range (months): treatment group 1 (37, 3 to 191); treatment group 2 (31, 3 to 131)
- Sex (M/F): treatment group 1 (33/172); treatment group 2 (53/125)
- Uropathy (VUR): treatment group 1 (73); treatment group 2 (70)
- Exclusion criteria
  * Primary: severely ill children; pseudomonas, staph or Group D Strep UTI; fever > 38°C for > 4 days
  * Secondary: recurrence of APN before DMSA at 6 to 9 months; VUR > grade 3

Interventions	Treatment group 1 • IV netilmicin: 7 mg/kg/d, days 1 and 2 • IV ceftriaxone: 50 mg/kg/d, days 1, 2 and 3 • Oral antibiotics: days 4 to 8 (5 days) according to sensitivity • Total 8 days Treatment group 2 • IV netilmicin: 7 mg/kg/d, days 1 and 2 • IV ceftriaxone: 50 mg/kg/d, days 1 to 8
Outcomes	• Scarring on DMSA at 6 months
Notes	• Definition of APN: UTI + fever > 38°, CRP > 20 mg/L • 165/548 (30%) excluded for loss to follow-up (87), APN recurrence (32), uropathy (16), No DMSA performed (30)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation (random tables) was centralised and stratified by centre by blocks of 20 numbered sealed opaque envelopes with equal numbers of treatment assignments"
Allocation concealment (selection bias)	Low risk	Allocation was done by local investigator by opening a numbered sealed envelope 48 hours after admission and after informed consent by the parents"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome (DMSA scan) assessed by 4 independent physicians without knowledge of treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	117/300 (23%) were lost to follow-up or refused DMSA after secondary exclusions made. Could influence results
Selective reporting (reporting bias)	High risk	No information on clinical or bacteriologic cure or adverse effects
Other bias	High risk	Supported by grants from Roche Laboratory and French Ministry of Health

Carapetis 2001

Methods	• Study design: parallel RCT • Study duration: March 1994 to January 1997 • Duration of follow-up: 2 months • Power analysis: 87/group to show 1 day difference in fever duration
Participants	• Country: Australia • Setting: tertiary centre IP • Children aged 1 month to 12 years; were ill, vomiting and unable to take oral medication reliably; UTI was diagnosed by identifying uropathogens in suprapubic aspirate specimens or a pure growth of ≥ 10^8 bacteria/L (= 10^5/mL) • Urine samples: MSU, catheter, SPA • Number: treatment group 1 (90); treatment group 2 (89) • Median age, IPR (years): treatment group 1 (1, 0.4 to 6.0); treatment group 2 (1, 0.4 to 4.6) • Sex (M/F): treatment group 1 (27/63); treatment group 2 (30/59) • Known uropathy/VUR detected: treatment group 1 (24/22); treatment group 2 (19/26) • Exclusion criteria: allergy to aminoglycoside, renal, hearing, vestibular dysfunction, neutropenia/immunodeficiency
Interventions	Treatment group 1 • Daily IV gentamicin: < 5 years: 7.5 mg/kg/d; 5-10 years: 6 mg/kg/d; > 10 years: 4.5 mg/kg/d; for 3.0 days (range 2 to 4) Treatment group 2 • IV gentamicin: same total dose each day as group 1 but given in three divided doses for 2.7 days (range 2 to 3.3)
Outcomes	• Resolution of clinical problem • Infective or non-infective sequelae • Persistent bacteriuria at end of gentamicin • Adverse effects
Notes	• Definition of APN: UTI and fever, vomiting, inability to take oral therapy • 5/184 excluded because did not satisfy entry criteria. None of 179 excluded from clinical analysis; 60/179 (33.5%) did not have follow-up urine culture & excluded from bacteriological outcome assessment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation stratified for age < 2 years and ≥ 2 years
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label study. Knowledge of treatment group could influence management
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label study. Primary outcome of clinical response could be influenced by knowledge of treatment group. "Audiology, bacteriology and biochemistry personnel were blinded to treatment status"

Carapetis 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	None of 179 excluded from primary outcome of clinical response
Selective reporting (reporting bias)	Low risk	Reported expected outcomes (clinical and bacteriologic eradication, adverse effects)
Other bias	Unclear risk	No information provided

Cheng 2006

Methods	• Study design: parallel RCT • Study duration: January 2003 to December 2004 • Duration of follow-up: 6 months • Power analysis: NS
Participants	• Country: Taiwan • Setting: tertiary centre IP • Children aged 0 months to 16 years; UTI plus CT findings of lobar nephronia following US showing nephromegaly and/or focal renal mass • Urine samples: most collected by MSU, SPA or catheter • Number: treatment group 1 (39); treatment group 2 (41) • Mean age ± SD (years): treatment group 1 (4.16 ± 4.22); treatment group 2 (3.72 ± 4.14) • Sex (M/F): treatment group 1 (16/23); treatment group 2 (17/24) • VUR detected: treatment group 1 (11/29); treatment group 2 (16/40) • Exclusion criteria: uncomplicated APN
Interventions	Treatment group 1 • 3 weeks duration of IV and oral antibiotics • Antibiotic used depended on sensitivities • IV changed to oral 2 to 3 days after fever had ceased Treatment group 2 • 2 weeks duration of IV and oral antibiotics • Antibiotic used depended on sensitivities • IV changed to oral 2 to 3 days after fever had ceased
Outcomes	• Bacteriological persistent/relapse • Persistence/recurrence of symptoms • Duration of fever
Notes	• Lobar nephronia (acute focal bacterial nephritis) diagnosed on CT but specific findings NS • Information from the authors: All children completed follow-up. Information on risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Randomly allocated with serial entry"

Cheng 2006 *(Continued)*

Allocation concealment (selection bias)	High risk	Patients allocated alternately to each group (information from the authors)
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical assessment
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding. Lack of blinding could influence outcome assessment of clinical symptoms
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. Information confirmed by authors
Selective reporting (reporting bias)	High risk	No reporting of adverse effects. Incomplete data on clinical symptom resolution
Other bias	Unclear risk	No information provided

Chong 2003

Methods	• Study design: parallel RCT • Study duration: January 2000 to May 2001 • Duration of follow-up: 3 months • Power calculation: 220 to show 10% difference in UTI cure with 80% power
Participants	• Country: Singapore • Setting: tertiary centre IP • Children aged I month to 13 years; UTI confirmed on 2 clean catch urine samples (single organism > 100,000/mL) or 1 catheter specimen (single organism > 1,000/mL) • Number: treatment group 1 (84); treatment group 2 (88)84 (40F) • Mean age ± SD (years): treatment group 1 (0.95 ± 1.25); treatment group 2 (0.90 ± 1.36) • Sex (M/F): treatment group 1 (44/40); treatment group 2 (41/47) • VUR: treatment group 1 (21, 11 no MCU); treatment group 2 (21, 15 no MCU) • Exclusion criteria: known obstructive uropathy; aminoglycoside or other nephrotoxic agent in previous month; allergy to aminoglycoside; renal or hearing impairment (including abnormal baseline OAE)
Interventions	Treatment group 1 • IV gentamicin: 5 mg/kg/d daily till resolution of fever (3.7 ±1.8 days) Treatment group 2 • IV gentamicin: 6 mg/kg/d 8 hourly till resolution of fever (3.5 ± 1.8 days)
Outcomes	• Negative urine culture at end of gentamicin • Time to resolution of fever • Nephrotoxicity (increase in creatinine by 50% or more) • Ototoxicity (loss of 30 dB or more on repeat OAE test and confirmed on brain auditory evoked response • Kidney scars on DMSA scan at 3 months
Notes	• Definition of UTI: fever > 38°C, pyuria > 200/mL or offensive urine, dysuria, frequency, loin pain

Chong 2003 *(Continued)*

- Post randomisation exclusions: No UTI (23), protocol violation (10), abnormal baseline OAE hearing test
- 38/210 excluded from analysis: no UTI (23); resistant to gentamicin (1); abnormal baseline hearing (4); protocol violation (10)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical assessment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but primary outcome was a laboratory result (negative urine culture) and unlikely to influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	15 (8%, excluding patients without UTI) were excluded from analysis (not including patients without UTI). This is unlikely to influence results
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	Funded by KK Women's and Children's Hospital RAU Grant 029/1999

Fischbach 1989

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 21 days • Power calculation: NS
Participants	• Country: France • Setting: tertiary centre IP • Children presenting with UTI (urinary leucocyte count >10 WBC/mm^3 and bacteriuria greater than or equal to 100,000 colonies/mL); a predominant isolate (more than 80% of the flora), with tissue penetration; clinically poor general condition; lumbar or abdominal pain; temperature > 38.5°C; ESR > 35 mm at 1 h; elevated CRP and orosomucoid • Urine collection: NS • Number: treatment group 1 (10); treatment group 2 (10) • Age: treatment group 1 (≤ 6 years (6); > 6 years (4)); treatment group 2 (≤ 6 years (6); > 6 years (4)) • Sex (M/F): treatment group 1 (3/7); treatment group 2 (2/8) • Known uropathy: treatment group 1 (1); treatment group 2 (1) • Exclusion criteria: allergy to B-lactam antibiotics; UTI post operatively; antibiotics in previous 72 hours; creatinine > 0.2 mmol/L

Fischbach 1989 *(Continued)*

Interventions	Treatment group 1 • IV cefotaxime: 25 mg/kg/dose, 4 doses/d for 14 days Treatment group 2 • IV amox/clav: 25 mg/kg/dose, 4 doses/d for 1 to 7 • Oral amox/clav: 50 mg/kg/d days 8 to 14
Outcomes	• Time to fever resolution • Persistent bacteriuria at 48 to 72 hours • Recurrent UTI at 7 days after completing therapy
Notes	• Definition of APN: UTI and fever > 38.5°C, loin pain, poor clinical condition, elevated CRP, ESR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation table used
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and clinical management could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding and primary clinical outcome assessment could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes are included
Other bias	Unclear risk	No information provided

Francois 1997

Methods	• Study design: parallel RCT • Study duration: • Duration of follow-up: 1 month • Power calculation: NS
Participants	• Country: France • Setting: multicentre tertiary centres IP • Children aged 6 months to 10 years • Urine collection: NS • Number (randomised/efficacy/safety): treatment group 1 (70/63/67); treatment group 2 (77/65/72)

Francois 1997 *(Continued)*

- Mean age ± SD (years): treatment group 1 (3.9 ± 2.9); treatment group 2 (4.3 ± 2.7)
- Sex (M/F): treatment group 1 (6/57); treatment group 2 (8/57)
- VUR: treatment group 1 (26); treatment group 2 (25)
- Exclusion criteria: Previous APN; organisms resistant to study antibiotics; allergy to cephalosporins, B-lactams, aminoglycosides; known uropathology; need for IV antibiotics based on ultrasound; kidney failure; immune deficiency; other infection

Interventions	Treatment group 1 • IV ceftriaxone: 50 mg/kg/d, daily dose for days 1 to 4 • IV netilmicin: 6 to 7.5 mg/kg/d in 3 divided doses for days 1 to 4 • Oral cefixime: 4 mg/kg/dose, 2 doses/d for days 5 to 10 Treatment group 2 • V ceftriaxone: 50 mg/kg/d, daily dose for days 1 to 4 • IV netilmicin: IV 6 to 7.5 mg/kg/d in 3 divided doses for days 1 to 4 • IV ceftriaxone: 50 mg/kg/d as single dose for days 5 to 10
Outcomes	• Persistent bacteriuria 2 days after end of therapy • Recurrent UTI in 20 days after therapy • Adverse events
Notes	• Definition of APN: UTI and fever > 38°C, pyuria, CRP increased • 19/147 (13%) excluded from efficacy analysis as did not have UTI

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random list
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Clinical management and assessment could be influenced by blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but outcomes evaluated by a scientific committee so unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients with positive urine cultures evaluated for efficacy
Selective reporting (reporting bias)	Low risk	Expected outcomes included
Other bias	Unclear risk	No information provided

Fujii 1987

Methods	• Study design: parallel RCT • Study duration: unclear • Duration of follow-up: unclear • Power analysis: NS
Participants	• Country: Japan • Setting: multicentre tertiary centres IP • Urine collection: NS • Number: treatment group 1 (54); treatment group 2 (51) • Age: NS • Sex (M/F): NS • Exclusion criteria: NS
Interventions	Treatment group 1 • Ampicillin suppositories: 1 g, 6 hourly for 5 days Treatment group 2 • Oral ampicillin: 1 g, 6 hourly for 5 days
Outcomes	• Clinical response • Eradication of causative organism
Notes	• APN: not defined • Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical assessment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding and unclear whether clinical or laboratory outcomes were primary
Incomplete outcome data (attrition bias) All outcomes	Low risk	Expected outcomes reported
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	Unclear risk	No information provided

Grimwood 1988

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 6 weeks • Power analysis: NS
Participants	• Country: New Zealand • Setting: tertiary centre IP and OPD • Urine collection: SPA or 2 consecutive MSU • Number: treatment group 1 (39); treatment group 2 (30) • Mean age (range): 4.9 years (range 2 weeks to 12 years) • Sex (M/F): 17/52 • Uropathy/VUR: 26/10 • APN: treatment group 1 (14); treatment group 2 (10) • Exclusion criteria: NS
Interventions	Treatment group 1 • IV gentamicin: 3 mg/kg single dose Treatment group 2 • 7 days of antibiotic according to sensitivity: TMP/SMX (16); amoxicillin (11); cephalosporins (3)
Outcomes	• Persistent bacteriuria 1 day after therapy • Relapse within 1 week of end of therapy • Recurrent UTI 1-6 weeks after end of therapy
Notes	• Definition of APN: UTI and fever > 38°C, loin pain, systemic effects • Study included 24 children with APN and 45 with cystitis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Each child was randomly allocated by random numbers to two treatment groups". Not stratified by clinical presentation
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but primary outcome was laboratory based and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed study
Selective reporting (reporting bias)	High risk	No results provided on clinical resolution or adverse events

Grimwood 1988 *(Continued)*

Other bias	Low risk	National Children's Health Research Foundation

Hoberman 1999

Methods	• Study design: parallel RCT • Study duration: January 1992 and July 1997 • Duration of follow-up: 7 months • Power calculation: 128/group to detect difference of 15% in kidney scarring
Participants	• Country: USA • Multicentre (3) tertiary centre IP and ED • Children aged 1 month to 2 years; rectal temperature of ≥ 38.3°C at presentation or within 24 hours, were suspected to have a UTI because of the presence of pyuria and bacteriuria; a positive urine culture from a specimen obtained by catheter • Urine collection: catheter • Number: treatment group 1 (153); treatment group 2 (153) • Mean age ± SD (years): treatment group 1 (8.8 ± 5.9); treatment group 2 (8.3 ± 5.6) • Sex (M/F): treatment group 1 (17/136); treatment group 2 (16/137) • VUR: treatment group 1 (61); treatment group 2 (54) • Exclusion criteria: clinically unstable patients; previous UTI; known uropathy; allergy to cephalosporins; other infections; gram positive cocci on stained urine
Interventions	Treatment group 1 • Oral cefixime: 16 mg/kg on day 1 then 4 mg/kg/dose, 2 doses/d for 13 days Treatment group 2 • IV cefotaxime: 50 mg/kg/dose, 4 doses/d for 3 days or till afebrile for 24 hours • Oral cefixime: 16 mg/kg following IV cefotaxime for 1 day then 4 mg/kg/dose, 2 doses/d for 13 days
Outcomes	• Scarring on DMSA at 6-7 months after UTI • Recurrent UTI in 6 months • Duration of fever
Notes	• Definition of APN: UTI and fever > 38.3°C

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were randomized at each site based on age and duration of fever"
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Clinical management could be influenced by lack of blinding
Blinding of outcome assessment (detection bias)	Low risk	Blinding of radiologists, who assessed DMSA scans. Short term outcome (urine culture) was laboratory based and unlikely to be affected by blinding

Hoberman 1999 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	34/306 (11%) no follow-up DMSA scans
Selective reporting (reporting bias)	High risk	No information on adverse effects
Other bias	High risk	Supported by Lederle/Wyeth-Ayerst Laboratories and by NIH grants

Kafetzis 2000

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 6 months • Power calculation: NS
Participants	• Country: Greece • Setting: tertiary centre IP • Children aged 1 month to 12 years; APN requiring IV antibiotics • Urine collection: SPA, catheter or 2 clean catch specimens • Number: Treatment group 1 (10): treatment group 2 (6) • Median age (range): 3 months (1 to 84 months) • Sex (M/F): 6/10 • Uropathy: 4 • Exclusion criteria: allergy to aminoglycosides, renal, hearing or vestibular dysfunction, antibiotics in previous 4 weeks, resistance to aminoglycosides
Interventions	Treatment group 1 • IV isepamicin: 7.5 mg/kg/dose, 2 doses/d for 10 to 14 days Treatment group 2 • IV amikacin: 7.5 mg/kg/dose, 2 doses/d for 10 to 14 days Co-interventions • Both agents were administered either solely or in combination with an appropriate antimicrobial agent
Outcomes	1. Persistent bacteriuria 7 days after end of therapy. 2. UTI 30 days after end of therapy. 3. Adverse events.
Notes	• Definition of APN: UTI and fever > 38°C, systemic or local symptoms, CRP > 30 mg/L, elevated ESR, WBC, pyuria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. 2:1 ratio

Kafetzis 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical assessment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary efficacy outcome was laboratory based and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed study
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Sponsored by Schering-Plough Research

Khan 1981

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 2 months • Power calculation: No
Participants	• Country: USA • Setting: tertiary centre, OPD • Children aged 6 month to 15 years • Urine collection: 2 consecutive clean catch specimens with positive culture (> 10^5 CFU/mL) • Number: treatment group 1 (27); treatment group 2 (27) • Mean age ± SEM (years): treatment group 1 (5.5 ± 0.6); treatment group 2 (5.8 ± 0.5) • Sex (M/F): treatment group 1 (2/25); treatment group 2 (2/25) • Exclusion criteria: urinary tract malformation or abnormal creatinine
Interventions	Treatment group 1 • Oral antibiotic: ampicillin, cephalexin or sulphisoxazole 4 times/d for 3 days Treatment group 2 • Oral antibiotic: ampicillin, cephalexin or sulphisoxazole 4 times/d for 10 days
Outcomes	• Absence of recurrence by 2 months (bacteriological) • Recurrence of UTI within 2 months
Notes	• Definition of APN: temperature > 38°C with/without other symptoms

Risk of bias

Bias	Authors' judgement	Support for judgement

Khan 1981 *(Continued)*

Random sequence generation (selection bias)	High risk	Episodes of UTI "treated prospectively on a random basis alternately"
Allocation concealment (selection bias)	High risk	Episodes of UTI "treated prospectively on a random basis alternately"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical assessment. Patients retrospectively divided into APN, lower UTI or asymptomatic
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary efficacy outcome was laboratory based and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if all patients completed the study
Selective reporting (reporting bias)	High risk	No information on adverse effects. Data only available as the number of episodes of APN
Other bias	Unclear risk	No information provided

Levtchenko 2001

Methods	• Study design: parallel RCT • Study duration: December 1995 to December 1998 • Duration of follow-up: 6 months • Power calculation: NS
Participants	• Country: Belgium • Setting; tertiary centre, IP/OPD • Children aged 6 weeks to 15 years; severely ill; fever ≥ 38.3°C associated with variable combinations of clinical signs ; biological alterations (sedimentation rate > 30 mm/h, increased CRP, leukocyte count > 15,000 with more than 50% neutrophils), and urinalysis revealing abnormal amounts of leukocytes (> 5 WBC/mm^3) and/or bacteria; absence of other focal infection • Urine collection: SPA, MSU, 2-3 consecutive bag specimens • Number: treatment group 1 (43); treatment group 2 (44) • Median age, range (months): treatment group 1 (25, 2 to 182); treatment group 2 (20, 3 to 179) • Sex (M/F): NS • Uropathy: treatment group 1 (5); treatment group 2 (1) • Exclusion criteria: negative urine culture; resistant organisms; severe uropathies; fever > 38°C within 24 hours of randomisation
Interventions	Both groups given temocillin IV 3 days and then randomised Treatment group 1 • IV temocillin: for further 4 days; dose (NS) • Oral amoxicillin or amox/clav: 50 mg/kg/dose, 3 doses/d for further 14 days Treatment group 2 • Oral amoxicillin or amox/clav: 50 mg/kg/dose, 3 doses/d for 18 days

Levtchenko 2001 *(Continued)*

Outcomes	• Persistent bacteriuria on day 7 of treatment • Recurrent UTI in 6 weeks after randomisation • Persistence of changes on DMSA at 6 months
Notes	• Definition of APN: UTI and fever > 38.3°C at start of IV therapy (afebrile at randomisation), systemic symptoms, loin pain, elevated WBC, ESR, CRP • 5 (5.4%) of 92 patients were excluded: intolerance to oral medication (1), error in randomisation (1), no follow-up at 6 months (3)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Clinical assessment could be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding Primary outcome of kidney scarring; DMSA scans reviewed without knowledge of treatment assignment. Primary outcome of urine culture: laboratory based and unlikely to affected by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 (5.4%) of patients did not complete follow-up. Unlikely to influence outcome
Selective reporting (reporting bias)	High risk	No detailed information on clinical response or adverse effects
Other bias	Unclear risk	No information provided

Marild 2009

Methods	• Study design: parallel RCT • Study duration: June 1996 to February 2001 • Duration of follow-up: 30 days • Power calculation: 256 and 128 required for each group for a difference in treatment response ≤ 8%
Participants	• Country: Sweden • Setting: multicentre (7) tertiary IP/OPD • Children aged 1 month to 12 years; first febrile UTI; Fever ≥ 38.5° in last 24 hours with/without abdominal pain, vomiting, flank pain; CRP ≥ 20 mg/L • Urine collection: SPA, MSU, bag specimens • Number: treatment group 1 (255); treatment group 2 (128) • Median age, range (years): treatment group 1 (0.9, 0.09 to 10.6); treatment group 2 (0.8, 0.09 to 7.3)

Marild 2009 *(Continued)*

	• Sex (M/F): treatment group 1 (187/68); treatment group 2 (90/38) • Exclusion criteria: Previous treatment for UTI; antibiotics in previous 7 days; needing IV therapy; known uropathy; hypersensitive to medications
Interventions	Treatment group 1 • Oral ceftibuten: 9 mg/kg once/d for 10 days Treatment group 2 • Oral TMP/SMX: 3 mg/15 mg/kg twice/d for 10 days
Outcomes	• Bacteriological elimination after treatment without recurrence • Clinical resolution • Adverse events
Notes	• APN: Fever ≥ 38.5°, abdominal pain, vomiting, flank pain, CRP ≥ 20 mg/L • Primary exclusions: 127/547 (23%) excluded (no bacteriuria 101, did not fulfil entry criteria 26) • Secondary exclusions: 37/420 (9%) not evaluable (no follow-up (29), on prophylaxis (8)) • ITT population 255/128. PP population 228/102

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated block randomisation stratified by gender. 2:1 allocation
Allocation concealment (selection bias)	Low risk	Sealed envelopes containing assigned treatment and randomisation number were opened in numerical order for eligible study patients
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label study. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	High risk	Clinical outcome assessment could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	9% of 420 patients excluded. Unlikely to influence results
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	High risk	Supported by grant from Schering-Plough

Montini 2007

Methods	• Study design: parallel RCT • Study duration: June 2000 to July 2005 • Duration of follow-up: 12 months • Power calculation: 220/group for 10% difference between groups

Montini 2007 *(Continued)*

Participants	• Country: Italy
	• Setting: multicentre tertiary centres (28)
	• Children aged 1 month to < 7 years; first episode of APN; normal antenatal ultrasound; 2 concordant urinalyses (> 25 WBC/μL) and 2 concordant urine cultures (> 100,000 CFU/mL) collected in sterile bags; at least 2 of fever ≥ 38°C, ESR ≥ 30 mm, CRP ≥ 3 times upper limit of normal, neutrophil count > normal for age
	• Number
	  * Evaluated for short-term outcomes: treatment group 1 (244); treatment group 2 (258)
	  * Completed the study: treatment group 1 (197); treatment group 2 (203)
	  * Repeat DMSA: treatment group 1 (109); treatment group 2 (114)
	• Mean age ± SD (months): treatment group 1 (12.7 ± 14.2); treatment group 2 (11.9 ± 13.9)
	• Sex (M/F): treatment group 1 (85/159); treatment group 2 (95/163)
	• Exclusion criteria: Severe clinical sepsis; dehydration, vomiting; allergy to study drugs; creatinine clearance < 70

Interventions	Treatment group 1 • Oral amox/clav: 50 mg/kg/d in three doses for 10 days Treatment group 2 • IV ceftriaxone: 50 mg/kg/d till resolution of fever • Oral amox/clav: 50 mg/kg/d to complete 10 day course
Outcomes	• Kidney parenchymal damage on DMSA scan at 1 year • Time to fever defervescence • Number with persistent bacteriuria at 72 hours • WBC, ESR, CRP at 72 hours
Notes	• Definition of APN: fever ≥ 38°C, high inflammation indices (WBC > normal for age, ESR ≥ 30 mm/h, CRP ≥ 3 times normal for age) • Children with no kidney parenchymal defects on first DMSA scan were not re-scanned at 1 year and assumed to have no scars at 1 year • Loss to follow-up: 102 (20.3%) of 502 did not complete study (13 did not have DMSA at entry, 89 did not undergo indicated DMSA at follow-up) • 177 patients with negative DMSA at entry, did not undergo follow-up scan and assumed to have no scar at follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated block randomisation with stratification by hospital, sex, age (< 2 years; ≥ 2years) at coordinating centre
Allocation concealment (selection bias)	Low risk	"Each participating centre received 4 series of 10 allocation codes in sealed and sequentially numbers opaque envelopes. The sequence was concealed until interventions assigned. Each participating centre allocated the children following a numeric order"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical assessment. "Could not blind group assignment because of the different routes of administration of the drug"
Blinding of outcome assessment (detection bias)	Low risk	Primary outcome was scarring on DMSA at 12 months. "Two nuclear physicians blinded to test results interpreted the scans independently"

Montini 2007 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up was 20.3% and could influence results
Selective reporting (reporting bias)	Low risk	Expected outcomes reported
Other bias	Low risk	Region of Veneto (research project 40/01) and Association Il Sogno di Stephano

Neuhaus 2008

Methods	• Study design: parallel RCT • Study duration: 1 July 2004 to 31 December 2004 • Duration of follow-up: 6 months • Power calculation: 98/group for 20% difference between groups
Participants	• Country: Switzerland. • Setting: multicentre tertiary hospital IP/OPD (5) • Children aged 6 months to 16 years; fever > 38.5°; abnormal urinalysis; with/without abdominal or flank pain; irritability; vomiting; diarrhoea; feeding difficulties. Included 152 with acute DMSA lesions who were evaluated with follow-up DMSA scans. Patients subsequently found not to have UTI or APN on DMSA were excluded • Urine collection: catheter • Number: treatment group 1 (80); treatment group 2 (72) • Median age, IQR (years): treatment group 1 (2.2, 0.9 to 4.9); treatment group 2 (1.6, 1.0 to 4.4) • Sex (M/F): treatment group 1 (8/72); treatment group 2 (10/62) • Exclusion criteria: complex kidney malformations; septic appearance; allergies to cephalosporins; immunosuppressive agents; impaired kidney function
Interventions	Treatment group 1 • Oral ceftibuten: 9 mg/kg once daily for 14 days Treatment group 2 • IV ceftriaxone: 50 mg/kg once daily for 3 days • Oral ceftibuten: 9 mg/kg once daily for 11 days
Outcomes	• Persistent lesions on second DMSA • Fever at day 3 • Resolution of UTI
Notes	• APN: UTI, fever 38°C , CRP > 10 mg/L, DMSA acute lesions • Primary exclusions: 146/365 (40%); no acute DMSA (19), no APN on DMSA (127) • Secondary exclusions: 67/219 (30%) for no follow-up DMSA • Additional information on methodology obtained from authors • Register of Swiss National Agency for therapeutic products Trial Number IKS 2001S03204

Risk of bias

Bias	Authors' judgement	Support for judgement

Neuhaus 2008 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer generated code. Independent clerk sealed and bundled blocks of 24 opaque sealed envelopes containing an equal number of assignments provided to centres
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes "so that people enrolling the patient into the study would not have known patient's assignment"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	DMSA scans read by investigators without knowledge of assignments
Incomplete outcome data (attrition bias) All outcomes	High risk	67/219 (30%) excluded from analysis as had no FU DMSA. This could influence results
Selective reporting (reporting bias)	High risk	No report of adverse effects
Other bias	High risk	Financial support from the Essex Company

Noorbakhsh 2004

Methods	• Study design: parallel RCT • Study duration: February 2003 to June 2003 • Duration of follow-up: 6 weeks • Power calculation: NS
Participants	• Country: Iran • Setting: single tertiary centre • Children aged 1 to 10 years; need for IV therapy; pathogen susceptible to study drug • Urine collection: strap on bags for infants; clean catch urine samples for older children • Number: treatment group 1 (24); treatment group 2 (30) • Age: NS • Sex (M/F): 11/43 • Exclusion criteria: allergy to study drugs; kidney obstruction/abscess; severe underlying disease/immunosuppressive therapy; other antibiotics required; abnormal LFTs/FBC; treated with IV antibiotics for 24 hours plus within 72 hours of baseline MSU; CKD stages 4, 5
Interventions	Treatment group 1 • IV ceftriaxone 50 mg/kg/d for 2 to 3 days • Oral cefixime: 8 mg/kg/d for 8 days Treatment group 2 • IV Amikacin 15 mg/kg/d or IV gentamicin 3 mg/kg/d with IV ampicillin 100 mg/kg/d for 10 days
Outcomes	• Clinical response at 3 to 5 days, end of therapy, 5 to 9 days after end of therapy and 4 to 6 weeks • Failure at 48 to 72 hours of therapy (urine culture with 10,000 organisms/mL of admission organism)

Noorbakhsh 2004 *(Continued)*

Notes	• APN: culture > 100,000 CFU/mL, fever, flank pain, costovertebral angle tenderness • Four patients did not complete follow-up and were not included in the study • Additional information obtained from authors on allocation concealment, follow-up and study definitions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Children were allocated alternately to each group (information from authors)
Allocation concealment (selection bias)	High risk	Children were allocated alternately to each group (information from authors)
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical management. "After 2-3 days of parenteral study therapy, investigators had the option to switch to oral cefixime if the patients had clinically improved". Unclear whether this referred to both treatment groups or whether patients in Group 1 could be continued on IV therapy for a longer duration.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding. Primary outcome of clinical response could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 (7%) patients did not complete follow-up and were excluded from the study
Selective reporting (reporting bias)	High risk	No report on adverse effects
Other bias	High risk	Pharmacist employed by Exir Pharmaceutical Co is study author

Pylkkänen 1981

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 12 months • Power calculation: NS
Participants	• Country: Finland • Setting: tertiary centre OPD • Children aged 0 to 13 years; 149 with upper tract UTI, 86 lower UTI (symptomatic (72); asymptomatic (14) • Urine collection: SPA or 2 consecutive MSU • Uropathy: 8 • Number: treatment group 1 (121); treatment group 2 (114) • Age: NS • Sex: NS • APN: treatment group 1 (73); treatment group 2 (76) • Exclusion criteria: NS
Interventions	Treatment group 1

Pylkkänen 1981 *(Continued)*

	• Oral sulfafurazole: 150 to 200 mg/kg/d in 3 doses for 10 days Treatment group 2 • Oral sulfafurazole: 150 to 200 mg/kg/d in 3 doses for 42 days
Outcomes	• Recurrent UTI during 12 months • Recurrent UTI by 1 month after ceasing therapy
Notes	• Definition of APN: UTI and fever > 39°C, ESR > 35, CRP > 20 mg/L • 271 entered study (10 lost to follow-up; 9 did not comply); 252 completed 2 years of follow-up of whom 235 (93%) evaluated (excluded - abnormal IVP (15); treatment error (2))

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. Not stratified for APN. "Patients were randomly divided.."
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding. Primary outcome was laboratory based and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	36/271 (13%) excluded.
Selective reporting (reporting bias)	High risk	No report of clinical resolution or adverse effects
Other bias	High risk	Supported by Foundation for Pediatric Research, Sigrid Juselius Foundation, Orion Pharmaceutical Co.

Repetto 1984

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 6 weeks • Power calculation: NS
Participants	• Country: Argentina • Setting: tertiary centre OPD • Children aged 1 month to 14 years; first or recurrent UTI • Urine collection: SPA, MSU • Number: treatment group 1 (18); treatment group 2 (19)18 (17F) • Median age (years): treatment group 1 (5); treatment group 2 (6)

Repetto 1984 *(Continued)*

	• Sex (M/F): treatment group 1 (2/16); treatment group 2 (4/15) • Uropathy: treatment group 1 (2); treatment group 2 (2) • APN: treatment group 1 (4); treatment group 2 (7) • Exclusion criteria: allergy to cephalosporins or penicillins; kidney failure; major uropathy
Interventions	Treatment group 1 • IV cefotaxime: 50 mg/kg single dose Treatment group 2 • Appropriate oral antibiotic for 10 days: TMP/SMX (14), nalidixic acid (2) nitrofurantoin (2), cephalexin (1), gentamicin (1)
Outcomes	• Persistent bacteriuria at 48 hours after end of treatment • Recurrent UTI at 30 days
Notes	• Definition of APN: UTI and fever > 38°C, loin pain • All participants completed follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided. "Patients..were treated randomly with either...). Not stratified for APN
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical management
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding. Primary outcomes were clinical and laboratory based. Clinical outcomes could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	High risk	No clinical outcomes reported
Other bias	Unclear risk	No information provided

Schaad 1998

Methods	• Study design: parallel RCT • Study duration: February 1996 to February 1997 • Duration of follow-up: 6 weeks • Power calculation: 150 patients/group to ensure difference in eradication rates < 12.6%
Participants	• Country: Europe (13 countries)

Schaad 1998 *(Continued)*

- Setting: multicentre tertiary centres IP (39)
- Children aged ≥1 month to 12 years; fever of at least 38.5°C; WBC > 15.000/mL; CRP > 30 µg/mL; evidence of pyuria; aged > 2 years to have one of the following: abdominal pain or tenderness, flank pain; or tenderness and dysuria
- Urine collection: SPA, catheter, MSU, 2 consecutive bags
- Number: treatment group 1 (149); treatment group 2 ()
- Evaluated for efficacy: treatment group 1 (115); treatment group 2 (120)
- Median age, range (years): treatment group 1 (1.7, 0.1 to 12.9); treatment group 2 (1.8, 0.1 to 11.8)
- Sex (M/F): treatment group 1 (32/83); treatment group 2 (37/83)
- Uropathy/VUR: treatment group 1 (53/33); treatment group 2 (56/33)
- Exclusion criteria: weight < 3 kg; previous investigational drug; allergy to B-lactams or arginine; kidney or liver dysfunction; immune deficiency

Interventions	Treatment group 1 • IV cefepime: 50 mg/kg/dose, 3 doses/d till afebrile for 48 hours • Oral TMP/SMX for 10 to 14 days or further IV therapy Treatment group 2 • IV ceftazidime: 50 mg/kg/dose, 3 doses/d till afebrile for 48 hours • Oral TMP/SMX for 10 to 14 days
Outcomes	• Persistent bacteriuria and unsatisfactory clinical response at end of IV therapy, end of antibiotic therapy • Recurrent UTI and unsatisfactory clinical response at 5 to 9 days and 4 to 6 weeks after end of therapy • Adverse effects
Notes	• Definition of APN: UTI and fever ≥ 38.5°C, WBC > 15,000 or CRP > 30 µg/mL and 1+ abdominal pain, loin pain, dysuria in children > 2 years • 299 enrolled; all assessed for safety; 235 evaluated for efficacy; 64 (21%) excluded from efficacy (no pathogen (40); treatment shorter than 12 days (13); improper dose (7): other (4))

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified by age (1 month to 2 years; > 2 years)
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical management. "Study drugs were administered in an open label manner"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Individual results were evaluated by blinded committee of experts"
Incomplete outcome data (attrition bias) All outcomes	Low risk	40/299 excluded for no pathogen; 24/259 (9%) excluded for other reasons but should have been included in analysis. 9% exclusions unlikely to influence outcomes. All patients included in safety analysis

Schaad 1998 *(Continued)*

Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	High risk	Biostatistics and data management by Bristol-Myers Squibb. Grant from Bristol-Myers Squibb

Toporovski 1992

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 5 weeks • Power calculation: NS
Participants	• Country: Brazil • Setting: Tertiary centre IP/OPD • Children aged 2 to 14 years; proven bacteriuria; at least 2 of the following: fever, dysuria, flank tenderness, urgency, and pyuria • Urine collection: MSU - 2 consecutive specimens • Number: treatment group 1 (26); treatment group 2 (11) • Age: treatment group 1 (); treatment group 2 () • Sex (M/F): treatment group 1 (10/16); treatment group 2 (3/8) • VUR: 6 • Exclusion criteria: resistant organisms; kidney or liver dysfunction; allergy to B-lactam antibiotics
Interventions	Treatment group 1 • Oral cefetamet pivoxil: 10 mg/kg/dose (18) or 20 mg/kg/dose (8), 2 doses/d for 7 to 10 days Treatment group 2 • Oral amox/clav: 30 to 50 mg/kg/dose, 3 doses/d for 7 to 10 days
Outcomes	• Persistent bacteriuria or unsatisfactory clinical response at end of therapy and at 4 to 5 weeks • Adverse effects
Notes	• Definition of APN: UTI and 2 + of fever ≥ 37.5°C, loin tenderness, dysuria, pyuria • Follow-up: all participants completed follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical management

Toporovski 1992 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	High risk	Supported by F. Hoffman-La Roche Ltd

Vigano 1992

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 6 weeks • Power calculation: Sample size chosen to detect 20% difference in effectiveness
Participants	• Country: Italy • Setting: tertiary centre IP • Children aged 1 month to 12 years; documented UTI and signs of pyelonephritis • Urine collection: clean catch or catheter • Number: treatment group 1 (74); treatment group 2 (70) • Mean age ± SD (years): treatment group 1 (2.01 ± 2.23); treatment group 2 (1.61 ± 2.14) • Sex (M/F): treatment group 1 (22/52); treatment group 2 (20/50) • Uropathy: treatment group 1 (18); treatment group 2 (23) • Exclusion criteria: allergy to aminoglycosides, renal or hearing dysfunction, neuropathic bladder, urinary diversion
Interventions	Treatment group 1 • IM netilmicin: 5 mg/kg/d in 1 dose for 10 days Treatment group 2 • IM netilmicin: 2 mg/kg/dose, 3 doses/d for 10 days
Outcomes	• Persistent bacteriuria at 7 days and recurrent UTI by 30 days after end of therapy • Adverse effects
Notes	• Definition of APN: UTI and fever > 38.5°C, ESR > 25, CRP > 20 mg/L • 144/150 enrolled were evaluated for efficacy and included. 6/144 (4%) excluded for inadequate follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated that patients were randomly allocated

Vigano 1992 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Stated that patients were randomly allocated
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding but primary outcome was laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/150 (4%) excluded from analysis. This is unlikely to influence results
Selective reporting (reporting bias)	High risk	No clinical outcomes reported
Other bias	Unclear risk	No information provided

Vilaichone 2001

Methods	• Study design: parallel RCT • Study duration: 1 January 1998 to 31 July 199 • Duration of follow-up: 6 months • Power calculation: NS
Participants	• Country: Thailand • Setting: Tertiary centre IP/OPD • Children aged 1 month to 15 years; fever, pyuria; positive urine culture, DMSA scan demonstrated cortical defect • Urine collection: MSU, bag • Number: treatment group 1 (18); treatment group 2 (18) • Mean age ± SD (months): treatment group 1 (26.7 ± 31.6); treatment group 2 (14.8 ± 21.08) • Sex (M/F): treatment group 1 (9/9); treatment group 2 (10/8) • VUR: treatment group 1 (3); treatment group 2 (4) • Exclusion criteria: age < 1 month; previous UTI; known uropathy; allergic to study antibiotics; kidney failure; chronic disease; antibiotics in previous 48 hours
Interventions	Treatment group 1 • IV ceftriaxone: 75 mg/kg/d in single dose till fever resolved • Oral ceftibuten: 9 mg/kg/d (dose frequency NS) • Total duration 10 days Treatment group 2 • IV ceftriaxone: 75 mg/kg/d in single dose for 10 days
Outcomes	• Abnormal DMSA at 6 months • Recurrent UTI during 6 months • Persistent bacteriuria at end of treatment

Vilaichone 2001 *(Continued)*

Notes	• Definition of APN: UTI and fever > 38°C, subnormal temperature in infants, acute defects on DMSA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized by blocks of four"
Allocation concealment (selection bias)	Unclear risk	Only information provided is "prospective randomized trial"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence clinical management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was DMSA scan results. "The site and number of lesions for each kidney were independently reported by 2 experienced nuclear medicine physicians"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed follow-up
Selective reporting (reporting bias)	High risk	Incomplete reporting of adverse effects
Other bias	Unclear risk	No information provided

Amox/clav - amoxicillin/clavulanic acid; APN - acute pyelonephritis; CKD - chronic kidney disease; CRP - C reactive protein; CT - computer tomography; DMSA - Tc99m-dimercaptosuccinic acid nuclear scan; ED - emergency department; ESR - erythrocyte sedimentation rate; IM - intramuscular; IP - inpatient; IQR - interquartile range; MSU - midstream urine specimen; NS - not stated; OAE - otoacoustic emission; OPD - outpatient department; SPA - suprapubic bladder aspiration; TMP/SMX - trimethoprim/sulphamethoxazole; US - ultrasound; UTI - urinary tract infection; VUR - vesicoureteric reflux; WBC - white blood count

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adam 1982	RCT; lower UTI
Avner 1983	RCT; lower UTI
Belet 2004	RCT; prophylaxis study
Bose 1974	Quasi-RCT; cannot separate data on children with pyelonephritis from those with lower UTI
Clemente 1994	RCT; immunomodulating agents not antibiotics in APN
Cox 1985	Adult data
Dagan 1992	RCT; cannot separate data on children with APN from those with lower UTI
Ellerstein 1977	RCT; unclear as to whether patients with APN included

Study	Reason for exclusion
Elo 1975	RCT; cannot separate data on children with APN from those with lower UTI
Fine 1985	RCT; lower UTI
Francois 1995	RCT; cannot separate data on children with APN from those with lower UTI
Garin 2006	RCT; prophylaxis study
Ginsburg 1982	RCT; cannot separate data on children with APN from those with lower UTI
Godard 1980	Not RCT
Gok 2001	RCT; cannot separate data on children with APN from those with lower UTI
Goldberg 1977	RCT; cannot separate data on children with APN from those with lower UTI
Helin 1978	Not RCT
Howard 1971	Not RCT
Howard 1978	RCT; cannot separate data on children with APN from those with lower UTI
Huang 2011	RCT comparing effect of methylprednisolone vs placebo on kidney scarring with same antibiotic regimen in each group
Iravani 1992	RCT; lower UTI
Ivanov 1999	RCT; does not compare antibiotic therapies
Kenda 1995	RCT; cannot separate data on children with APN from those with lower UTI
Kontiokari 2005	RCT; prophylaxis study
Kornberg 1994	RCT; lower UTI
Lake 1971	RCT; UTI but cannot separate data for febrile children from adult data
Lubitz 1984	RCT; cannot separate data on children with APN from those with lower UTI
Madrigal 1988	RCT; cannot separate data on children with APN from those with lower UTI
Moe 1977	RCT; cannot separate data on children with APN from those with lower UTI
Olbing 1970	RCT; prophylaxis study
Orekhova 2009	Study of non-antibiotic (immunological stimulating agent) as prophylaxis against UTI
Palcoux 1986	Not RCT
Petersen 1991	RCT; lower UTI
Piekkala 1985	Not RCT
Pitt 1982	RCT; cannot separate data on children with APN from those with lower UTI

Study	Reason for exclusion
Ray 1970	RCT; prophylaxis
Russo 1977	RCT; cannot separate data on children with APN from those with lower UTI
Sember 1985	RCT; cannot separate data on children with APN from those with lower UTI
Shapiro 1981	RCT; lower UTI
Thomas 1972	Not RCT
Vlatković 1972	Not RCT
Wallen 1983	RCT; lower UTI
Weber 1982	RCT; cannot separate data on children with APN from those with lower UTI

APN - acute pyelonephritis; RCT - randomised controlled trial; UTI - urinary tract infection

Characteristics of ongoing studies *[ordered by study ID]*

NCT00724256

Trial name or title	Short-term antibiotic therapy for pyelonephritis in childhood (STUTI)
Methods	Country: Italy, USA Tertiary hospital ED
Participants	Inclusion: children aged 1 month to 5 years with first episode of acute pyelonephritis Exclusions: children with vomiting/sepsis or other condition where oral antibiotics could not be given. Pyelonephritis with abscess. Allergy to ceftibuten. Antibiotic prophylaxis with antibiotic of same class
Interventions	Group1: oral ceftibuten 9 mg/kg once daily for 7 days Group 2: oral ceftibuten 9 mg/kg once daily for 10 days
Outcomes	1. Rate of kidney parenchymal damage at 6 to 12 months post UTI 2. Relapses of UTI 3. Adverse effect of therapy
Starting date	Start date: July 2006
Contact information	Maria Lazzerini, IRCCS Burlo Garofolo
Notes	Trial terminated because of patients' refusal of DMSA scans on follow-up

DMSA - Tc99m-dimercaptosuccinic acid nuclear scan; ED - emergency department; UTI - urinary tract infection

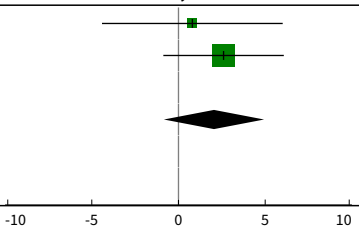
DATA AND ANALYSES

Comparison 1. Oral versus IV followed by oral (11 days) therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to fever resolution	2	808	Mean Difference (IV, Random, 95% CI)	2.05 [-0.84, 4.94]
2 Fever on Day 3	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Number with persistent UTI at 72 hours	2	542	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.07, 17.41]
4 Inflammatory markers at 72 hours	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 WCC [$\times 10^9$/L]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 ESR [mm/60 min]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 CRP [mg/L]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Recurrent UTI within 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Total UTIs	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Symptomatic UTIs	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Persistent kidney damage at 6-12 months	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 All included patients with acute pyelonephritis	4	943	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.59, 1.12]
6.2 Patients with kidney parenchymal damage on initial DMSA	4	681	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.61, 1.03]
7 Proportion of kidney parenchyma with damage at 6 months	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
8 Kidney damage at 6 months (post hoc subgroup analysis)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 Persistent damage in children with VUR	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Persistent damage in children without VUR	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 Persistent kidney damage with VUR grades 1-2	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.4 Persistent damage with VUR grades 3-5	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

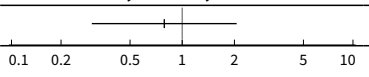
Analysis 1.1. Comparison 1 Oral versus IV followed by oral (11 days) therapy, Outcome 1 Time to fever resolution.

Study or subgroup	Oral therapy N	Oral therapy Mean(SD)	IV then oral therapy N	IV then oral therapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Hoberman 1999	153	24.7 (23.2)	153	23.9 (23.3)		30.77%	0.8[-4.41,6.01]
Montini 2007	244	36.9 (19.7)	258	34.3 (20)		69.23%	2.6[-0.87,6.07]
Total ***	**397**		**411**			**100%**	**2.05[-0.84,4.94]**
Heterogeneity: Tau^2=0; Chi^2=0.32, df=1(P=0.57); I^2=0%							
Test for overall effect: Z=1.39(P=0.17)							



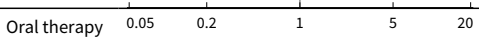
Analysis 1.2. Comparison 1 Oral versus IV followed by oral (11 days) therapy, Outcome 2 Fever on Day 3.

Study or subgroup	Oral therapy n/N	IV then oral therapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Neuhaus 2008	7/80	8/72		0.79[0.3,2.06]



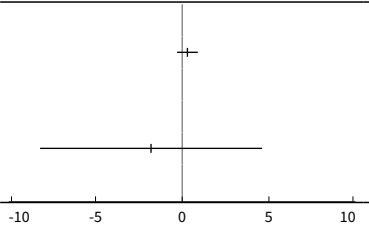
Analysis 1.3. Comparison 1 Oral versus IV followed by oral (11 days) therapy, Outcome 3 Number with persistent UTI at 72 hours.

Study or subgroup	Oral therapy n/N	IV then oral therapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Montini 2007	1/186	1/204		100%	1.1[0.07,17.41]
Neuhaus 2008	0/80	0/72			Not estimable
Total (95% CI)	**266**	**276**		**100%**	**1.1[0.07,17.41]**
Total events: 1 (Oral therapy), 1 (IV then oral therapy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.07(P=0.95)					

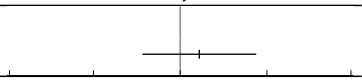


Analysis 1.4. Comparison 1 Oral versus IV followed by oral (11 days) therapy, Outcome 4 Inflammatory markers at 72 hours.

Study or subgroup	Oral therapy N	Oral therapy Mean(SD)	IV then oral therapy N	IV then oral therapy Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.4.1 WCC [×10^9/L]						
Montini 2007	230	9.8 (3.5)	243	9.5 (3.1)		0.3[-0.3,0.9]
1.4.2 ESR [mm/60 min]						
Montini 2007	170	50.8 (32)	168	52.6 (27.9)		-1.8[-8.2,4.6]

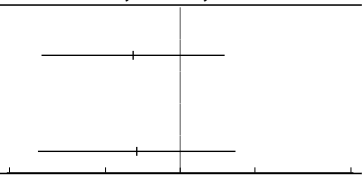


Study or subgroup	Oral therapy N	Oral therapy Mean(SD)	IV then oral therapy N	IV then oral therapy Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.4.3 CRP [mg/L]						
Montini 2007	235	9.3 (20.9)	251	8.2 (15.4)		1.1[-2.18,4.38]



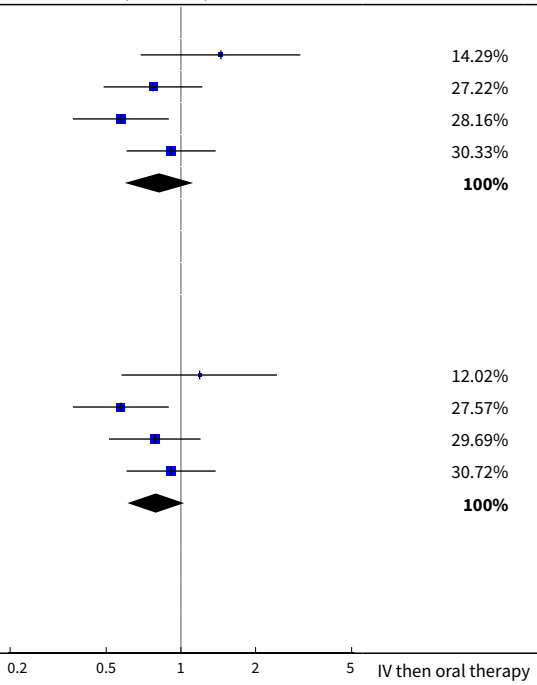
Analysis 1.5. Comparison 1 Oral versus IV followed by oral (11 days) therapy, Outcome 5 Recurrent UTI within 6 months.

Study or subgroup	Oral therapy n/N	IV then oral therapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.5.1 Total UTIs				
Hoberman 1999	8/140	13/147		0.65[0.28,1.51]
1.5.2 Symptomatic UTIs				
Hoberman 1999	7/140	11/147		0.67[0.27,1.67]

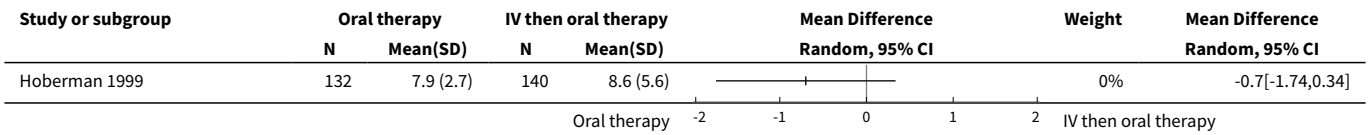


Analysis 1.6. Comparison 1 Oral versus IV followed by oral (11 days) therapy, Outcome 6 Persistent kidney damage at 6-12 months.

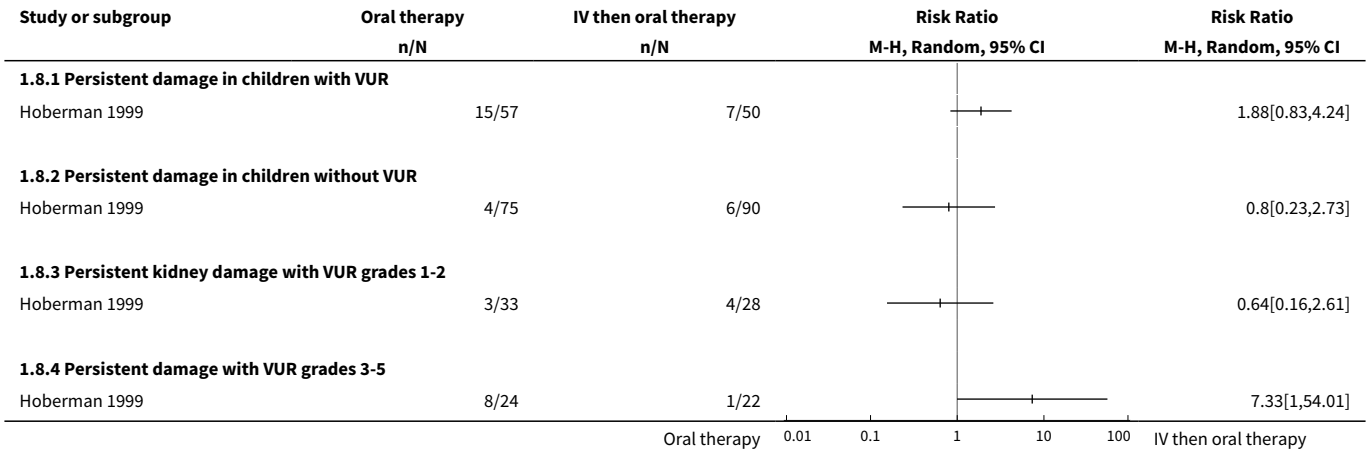
Study or subgroup	Oral therapy n/N	IV then oral therapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 All included patients with acute pyelonephritis					
Hoberman 1999	15/132	11/140		14.29%	1.45[0.69,3.03]
Montini 2007	27/197	36/203		27.22%	0.77[0.49,1.22]
Neuhaus 2008	21/80	33/72		28.16%	0.57[0.37,0.89]
Bocquet 2012	25/61	26/58		30.33%	0.91[0.6,1.38]
Subtotal (95% CI)	**470**	**473**		**100%**	**0.82[0.59,1.12]**
Total events: 88 (Oral therapy), 106 (IV then oral therapy)					
Heterogeneity: Tau^2=0.04; Chi^2=5.05, df=3(P=0.17); I^2=40.61%					
Test for overall effect: Z=1.24(P=0.22)					
1.6.2 Patients with kidney parenchymal damage on initial DMSA					
Hoberman 1999	15/100	11/87		12.02%	1.19[0.58,2.44]
Neuhaus 2008	21/80	33/72		27.57%	0.57[0.37,0.89]
Montini 2007	27/109	36/114		29.69%	0.78[0.51,1.2]
Bocquet 2012	25/61	26/58		30.72%	0.91[0.6,1.38]
Subtotal (95% CI)	**350**	**331**		**100%**	**0.79[0.61,1.03]**
Total events: 88 (Oral therapy), 106 (IV then oral therapy)					
Heterogeneity: Tau^2=0.01; Chi^2=3.7, df=3(P=0.3); I^2=18.93%					
Test for overall effect: Z=1.73(P=0.08)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.88), I^2=0%					



Analysis 1.7. Comparison 1 Oral versus IV followed by oral (11 days) therapy, Outcome 7 Proportion of kidney parenchyma with damage at 6 months.



Analysis 1.8. Comparison 1 Oral versus IV followed by oral (11 days) therapy, Outcome 8 Kidney damage at 6 months (post hoc subgroup analysis).



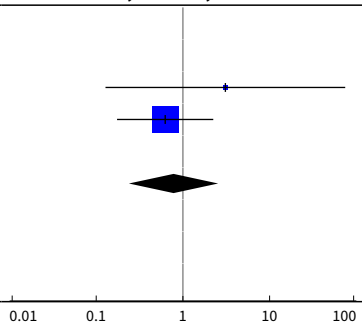
Comparison 2. Short duration (3-4 days) versus long duration (7-14 days) IV therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent bacteriuria after treatment	4	305	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.24, 2.55]
2 Recurrent UTI within 6 months	5	993	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.58, 1.62]
3 Persistent kidney damage at 3-6 months	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 All included patients with acute pyelonephritis	4	726	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.80, 1.29]
3.2 Patients with renal parenchymal damage on initial DMSA scan	3	315	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.84, 1.45]
4 Persistent kidney damage at 3-6 months (post hoc subgroup analysis)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 VUR present	2	81	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.69, 1.43]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.2 No VUR	2	173	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.81, 1.76]
4.3 Age less than 1 year	1	91	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.71, 3.01]
4.4 Age 1 year or over	1	129	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.59, 1.34]
4.5 Delay in treatment less than 7 days in individual kidneys	1	53	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.59, 3.92]
4.6 Delay in treatment of 7 days or more in individual kidneys	1	12	Risk Ratio (M-H, Random, 95% CI)	2.10 [0.92, 4.77]
5 Adverse effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Gastrointestinal effects	2	175	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.55, 3.05]

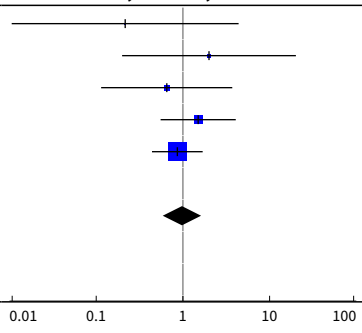
Analysis 2.1. Comparison 2 Short duration (3-4 days) versus long duration (7-14 days) IV therapy, Outcome 1 Persistent bacteriuria after treatment.

Study or subgroup	Short duration n/N	Long duration n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Levtchenko 2001	0/44	0/43			Not estimable
Vilaichone 2001	0/18	0/18			Not estimable
Francois 1997	1/63	0/65		13.88%	3.09[0.13,74.55]
Noorbakhsh 2004	3/24	6/30		86.12%	0.63[0.17,2.24]
Total (95% CI)	**149**	**156**		**100%**	**0.78[0.24,2.55]**
Total events: 4 (Short duration), 6 (Long duration)					
Heterogeneity: Tau^2=0; Chi^2=0.85, df=1(P=0.36); I^2=0%					
Test for overall effect: Z=0.41(P=0.68)					



Analysis 2.2. Comparison 2 Short duration (3-4 days) versus long duration (7-14 days) IV therapy, Outcome 2 Recurrent UTI within 6 months.

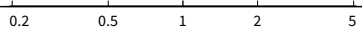
Study or subgroup	Short duration n/N	Long duration n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Francois 1997	0/49	2/53		2.88%	0.22[0.01,4.39]
Vilaichone 2001	2/18	1/18		4.89%	2[0.2,20.15]
Levtchenko 2001	2/44	3/43		8.62%	0.65[0.11,3.71]
Benador 2001	9/110	6/110		26.16%	1.5[0.55,4.07]
Bouissou 2008	15/277	17/271		57.45%	0.86[0.44,1.69]
Total (95% CI)	**498**	**495**		**100%**	**0.97[0.58,1.62]**
Total events: 28 (Short duration), 29 (Long duration)					
Heterogeneity: Tau^2=0; Chi^2=2.39, df=4(P=0.67); I^2=0%					



Study or subgroup	Short duration n/N	Long duration n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=0.1(P=0.92)					

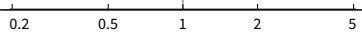
Analysis 2.3. Comparison 2 Short duration (3-4 days) versus long duration (7-14 days) IV therapy, Outcome 3 Persistent kidney damage at 3-6 months.

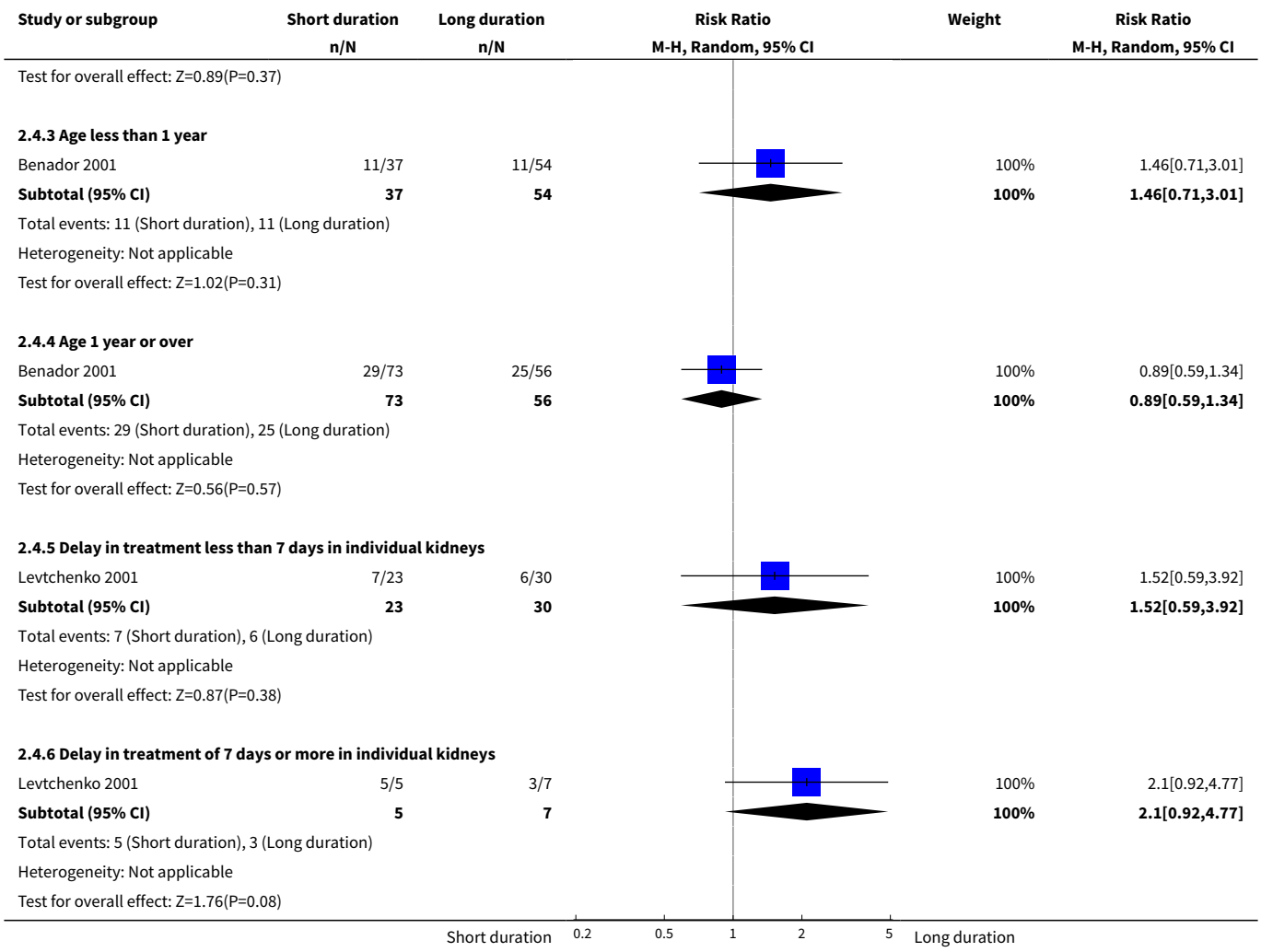
Study or subgroup	Short duration n/N	Long duration n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 All included patients with acute pyelonephritis					
Levtchenko 2001	11/44	8/43		8.75%	1.34[0.6,3.01]
Vilaichone 2001	12/18	11/18		23.56%	1.09[0.67,1.79]
Bouissou 2008	26/205	31/178		24.7%	0.73[0.45,1.18]
Benador 2001	40/110	36/110		42.99%	1.11[0.77,1.6]
Subtotal (95% CI)	**377**	**349**		**100%**	**1.01[0.8,1.29]**
Total events: 89 (Short duration), 86 (Long duration)					
Heterogeneity: Tau^2=0; Chi^2=2.66, df=3(P=0.45); I^2=0%					
Test for overall effect: Z=0.11(P=0.91)					
2.3.2 Patients with renal parenchymal damage on initial DMSA scan					
Levtchenko 2001	11/33	8/26		13.19%	1.08[0.51,2.3]
Vilaichone 2001	12/18	11/18		30.73%	1.09[0.67,1.79]
Benador 2001	40/110	36/110		56.08%	1.11[0.77,1.6]
Subtotal (95% CI)	**161**	**154**		**100%**	**1.1[0.84,1.45]**
Total events: 63 (Short duration), 55 (Long duration)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=2(P=1); I^2=0%					
Test for overall effect: Z=0.69(P=0.49)					



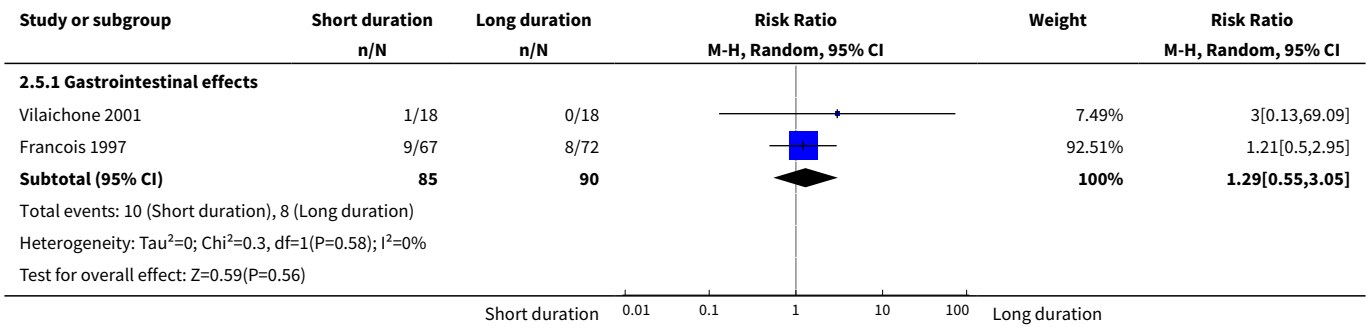
Analysis 2.4. Comparison 2 Short duration (3-4 days) versus long duration (7-14 days) IV therapy, Outcome 4 Persistent kidney damage at 3-6 months (post hoc subgroup analysis).

Study or subgroup	Short duration n/N	Long duration n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 VUR present					
Benador 2001	14/36	15/38		40.82%	0.99[0.56,1.74]
Vilaichone 2001	3/3	4/4		59.18%	1[0.62,1.6]
Subtotal (95% CI)	**39**	**42**		**100%**	**0.99[0.69,1.43]**
Total events: 17 (Short duration), 19 (Long duration)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.96); I^2=0%					
Test for overall effect: Z=0.03(P=0.97)					
2.4.2 No VUR					
Benador 2001	25/72	21/72		65.94%	1.19[0.74,1.92]
Vilaichone 2001	9/15	7/14		34.06%	1.2[0.62,2.34]
Subtotal (95% CI)	**87**	**86**		**100%**	**1.19[0.81,1.76]**
Total events: 34 (Short duration), 28 (Long duration)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.98); I^2=0%					





Analysis 2.5. Comparison 2 Short duration (3-4 days) versus long duration (7-14 days) IV therapy, Outcome 5 Adverse effects.

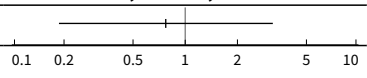


Comparison 3. Single dose parenteral therapy and oral therapy versus oral therapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent bacteriuria at 48 hours	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Treatment failure after 48 hours of therapy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Recurrent UTI within 1 month	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Gastrointestinal adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

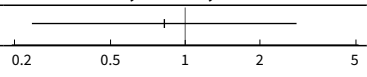
Analysis 3.1. Comparison 3 Single dose parenteral therapy and oral therapy versus oral therapy alone, Outcome 1 Persistent bacteriuria at 48 hours.

Study or subgroup	Ceftriaxone/TMP+SMX n/N	TMP+SMX n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Baker 2001	3/34	4/35		0.77[0.19,3.2]



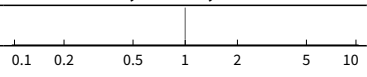
Analysis 3.2. Comparison 3 Single dose parenteral therapy and oral therapy versus oral therapy alone, Outcome 2 Treatment failure after 48 hours of therapy.

Study or subgroup	Ceftriaxone/TMP+SMX n/N	TMP+SMX n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Baker 2001	4/34	5/35		0.82[0.24,2.81]



Analysis 3.3. Comparison 3 Single dose parenteral therapy and oral therapy versus oral therapy alone, Outcome 3 Recurrent UTI within 1 month.

Study or subgroup	Ceftriaxone/TMP+SMX n/N	TMP+SMX n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Baker 2001	0/34	0/35		Not estimable



Analysis 3.4. Comparison 3 Single dose parenteral therapy and oral therapy versus oral therapy alone, Outcome 4 Adverse events.

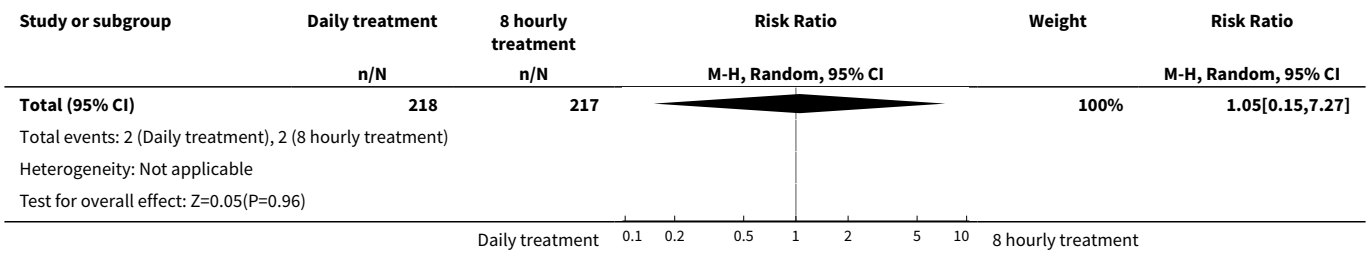
Study or subgroup	Ceftriaxone/TMP+SMX n/N	TMP+SMX n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.4.1 Total adverse events				
Baker 2001	4/34	3/35		1.37[0.33,5.68]
3.4.2 Gastrointestinal adverse events				
Baker 2001	3/34	3/35		1.03[0.22,4.75]

Comparison 4. Different dosing regimens of aminoglycosides (daily versus 8 hourly)

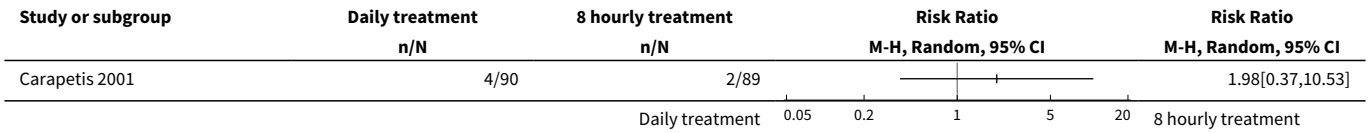
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent bacteriuria after 1-3 days of treatment	3	435	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.15, 7.27]
2 Persistent symptoms at end of 3 days of IV therapy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Persistent bacteriuria at 1 week after treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Reinfection at 1 month after completing treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Hearing impairment following treatment	3	271	Risk Ratio (M-H, Random, 95% CI)	2.83 [0.33, 24.56]
6 Increase in serum creatinine during treatment	3	419	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.20, 2.82]
7 Time to resolution of fever	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 Kidney parenchymal damage at 3 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Different dosing regimens of aminoglycosides (daily versus 8 hourly), Outcome 1 Persistent bacteriuria after 1-3 days of treatment.

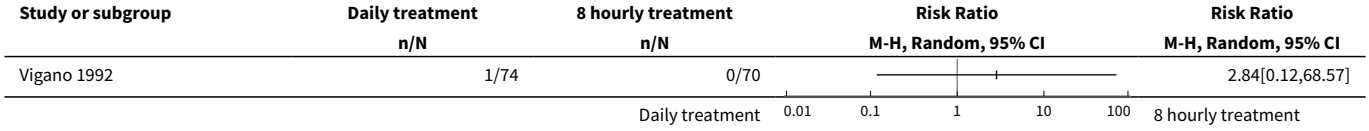
Study or subgroup	Daily treatment n/N	8 hourly treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Vigano 1992	0/74	0/70			Not estimable
Carapetis 2001	0/60	0/59			Not estimable
Chong 2003	2/84	2/88		100%	1.05[0.15,7.27]



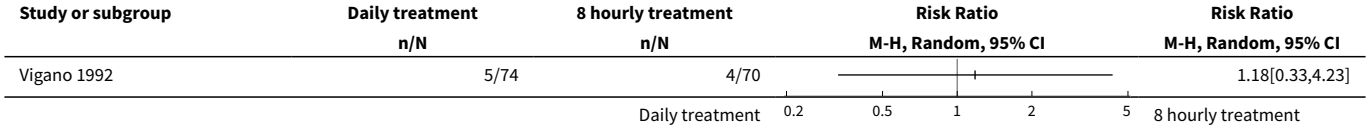
Analysis 4.2. Comparison 4 Different dosing regimens of aminoglycosides (daily versus 8 hourly), Outcome 2 Persistent symptoms at end of 3 days of IV therapy.



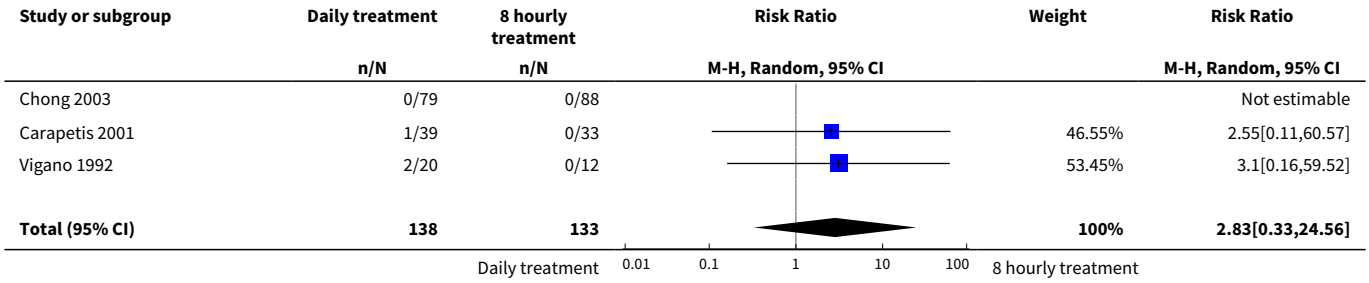
Analysis 4.3. Comparison 4 Different dosing regimens of aminoglycosides (daily versus 8 hourly), Outcome 3 Persistent bacteriuria at 1 week after treatment.



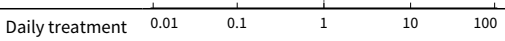
Analysis 4.4. Comparison 4 Different dosing regimens of aminoglycosides (daily versus 8 hourly), Outcome 4 Reinfection at 1 month after completing treatment.



Analysis 4.5. Comparison 4 Different dosing regimens of aminoglycosides (daily versus 8 hourly), Outcome 5 Hearing impairment following treatment.



Study or subgroup	Daily treatment n/N	8 hourly treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 3 (Daily treatment), 0 (8 hourly treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.93); I^2=0%					
Test for overall effect: Z=0.94(P=0.35)					

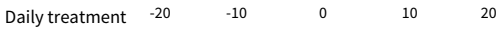


Analysis 4.6. Comparison 4 Different dosing regimens of aminoglycosides (daily versus 8 hourly), Outcome 6 Increase in serum creatinine during treatment.

Study or subgroup	Daily treatment n/N	8 hourly treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Carapetis 2001	1/64	1/52		22.97%	0.81[0.05,12.68]
Vigano 1992	2/74	2/70		46.43%	0.95[0.14,6.53]
Chong 2003	1/79	2/80		30.6%	0.51[0.05,5.47]
Total (95% CI)	**217**	**202**		**100%**	**0.75[0.2,2.82]**
Total events: 4 (Daily treatment), 5 (8 hourly treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.16, df=2(P=0.92); I^2=0%					
Test for overall effect: Z=0.42(P=0.67)					

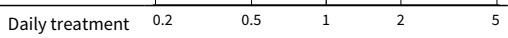
Analysis 4.7. Comparison 4 Different dosing regimens of aminoglycosides (daily versus 8 hourly), Outcome 7 Time to resolution of fever.

Study or subgroup	Daily treatment N	Daily treatment Mean(SD)	8 hourly treatment N	8 hourly treatment Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Chong 2003	84	47.4 (34.6)	88	45 (34.3)		2.4[-7.9,12.7]



Analysis 4.8. Comparison 4 Different dosing regimens of aminoglycosides (daily versus 8 hourly), Outcome 8 Kidney parenchymal damage at 3 months.

Study or subgroup	Daily treatment n/N	8 hourly treatment n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Chong 2003	18/75	23/71		0.74[0.44,1.25]

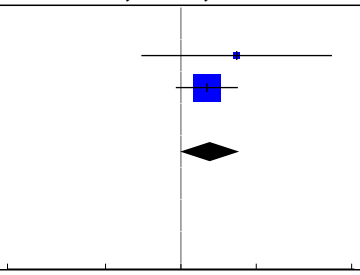


Comparison 5. Third generation cephalosporin versus other antibiotic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent bacteriuria	3	439	Risk Ratio (M-H, Random, 95% CI)	2.41 [0.98, 5.93]
2 Recurrent UTI after end of therapy	4	491	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.32, 4.74]
3 Persistent symptoms after end of treatment	3	471	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.13, 0.62]
4 Number with fever for more than 48 hours	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Recurrent bacteriuria at 4-6 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Recurrent symptomatic UTI at 4-6 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Gastrointestinal adverse events	4	591	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.34, 2.58]
8 Number discontinuing treatment for adverse effect	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

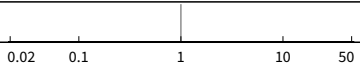
Analysis 5.1. Comparison 5 Third generation cephalosporin versus other antibiotic, Outcome 1 Persistent bacteriuria.

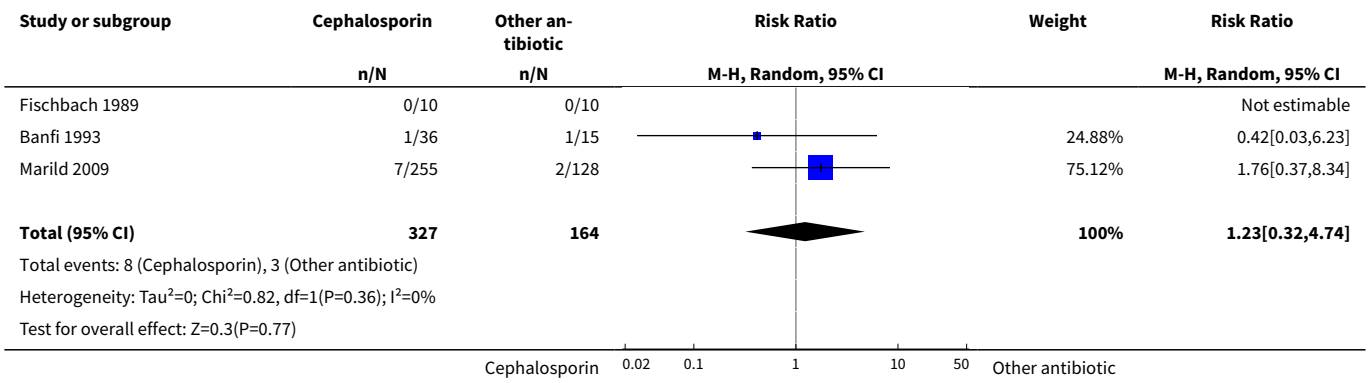
Study or subgroup	Cephalosporin n/N	Other antibiotic n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Toporovski 1992	0/26	0/11			Not estimable
Fischbach 1989	2/9	0/10		9.57%	5.5[0.3,101.28]
Marild 2009	22/255	5/128		90.43%	2.21[0.86,5.7]
Total (95% CI)	**290**	**149**		**100%**	**2.41[0.98,5.93]**
Total events: 24 (Cephalosporin), 5 (Other antibiotic)					
Heterogeneity: Tau^2=0; Chi^2=0.34, df=1(P=0.56); I^2=0%					
Test for overall effect: Z=1.91(P=0.06)					



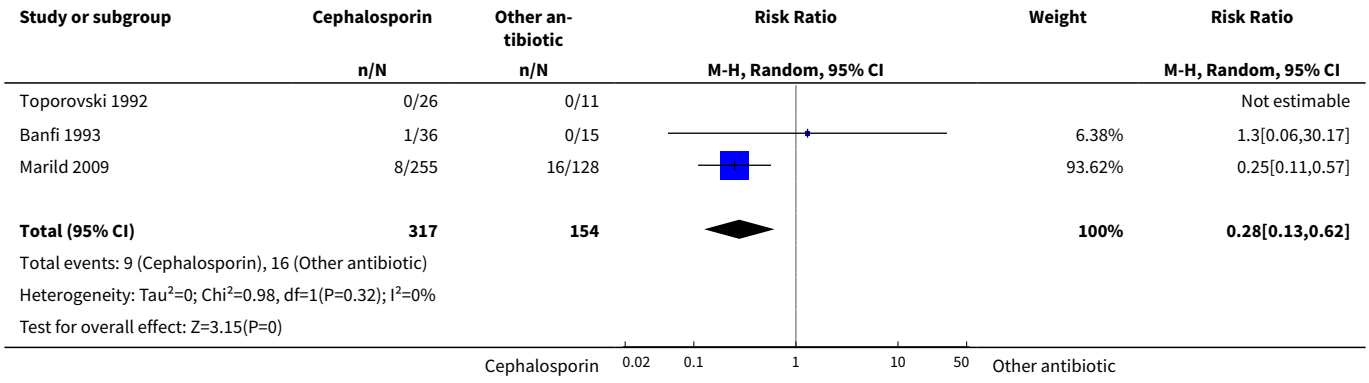
Analysis 5.2. Comparison 5 Third generation cephalosporin versus other antibiotic, Outcome 2 Recurrent UTI after end of therapy.

Study or subgroup	Cephalosporin n/N	Other antibiotic n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Toporovski 1992	0/26	0/11			Not estimable

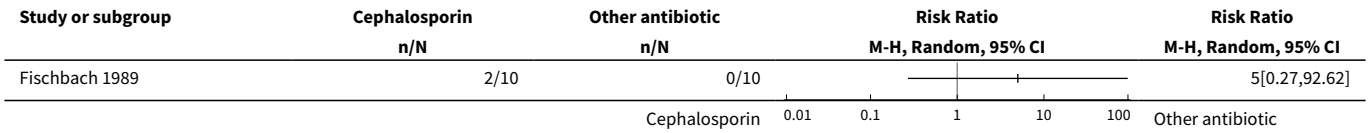




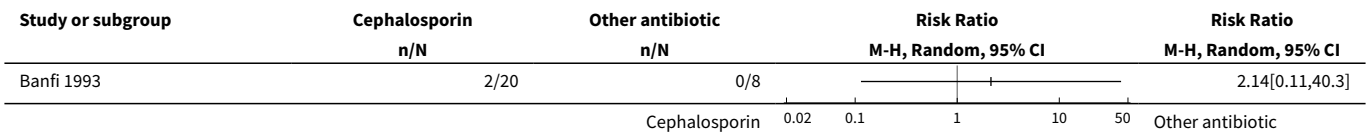
Analysis 5.3. Comparison 5 Third generation cephalosporin versus other antibiotic, Outcome 3 Persistent symptoms after end of treatment.



Analysis 5.4. Comparison 5 Third generation cephalosporin versus other antibiotic, Outcome 4 Number with fever for more than 48 hours.

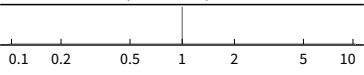


Analysis 5.5. Comparison 5 Third generation cephalosporin versus other antibiotic, Outcome 5 Recurrent bacteriuria at 4-6 weeks.



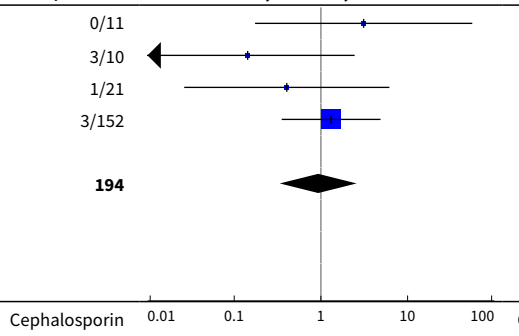
Analysis 5.6. Comparison 5 Third generation cephalosporin versus other antibiotic, Outcome 6 Recurrent symptomatic UTI at 4-6 weeks.

Study or subgroup	Cephalosporin n/N	Other antibiotic n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Banfi 1993	0/20	0/15		Not estimable



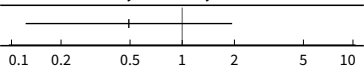
Analysis 5.7. Comparison 5 Third generation cephalosporin versus other antibiotic, Outcome 7 Gastrointestinal adverse events.

Study or subgroup	Cephalosporin n/N	Other antibiotic n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Toporovski 1992	3/26	0/11		12.54%	3.11[0.17,55.65]
Fischbach 1989	0/10	3/10		12.9%	0.14[0.01,2.45]
Banfi 1993	1/52	1/21		14.04%	0.4[0.03,6.16]
Marild 2009	8/309	3/152		60.52%	1.31[0.35,4.87]
Total (95% CI)	**397**	**194**		**100%**	**0.93[0.34,2.58]**
Total events: 12 (Cephalosporin), 7 (Other antibiotic)					
Heterogeneity: Tau^2=0; Chi^2=2.98, df=3(P=0.4); I^2=0%					
Test for overall effect: Z=0.14(P=0.89)					



Analysis 5.8. Comparison 5 Third generation cephalosporin versus other antibiotic, Outcome 8 Number discontinuing treatment for adverse effect.

Study or subgroup	Cephalosporin n/N	Other antibiotic n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Marild 2009	4/309	4/152		0.49[0.12,1.94]



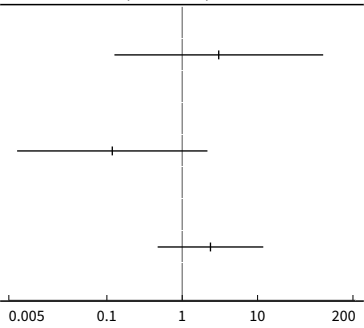
Comparison 6. Cefepime versus ceftazidime

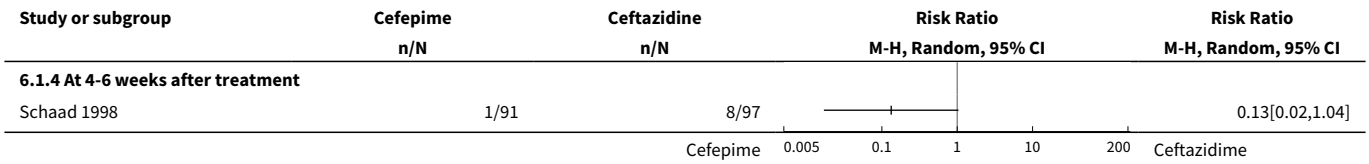
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistence or recurrence of initial pathogen	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 At end of IV therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 At the end of IV and oral therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 At 5-9 days after treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 At 4-6 weeks after treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Infection with new pathogen at 4-6 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Unsatisfactory clinical response	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 At end of IV therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 At end of IV and oral therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 At 5-9 days after treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 At 4-6 weeks after treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Drug-related adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Gastrointestinal adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.4 Cutaneous adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.5 Discontinuation due to drug related adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

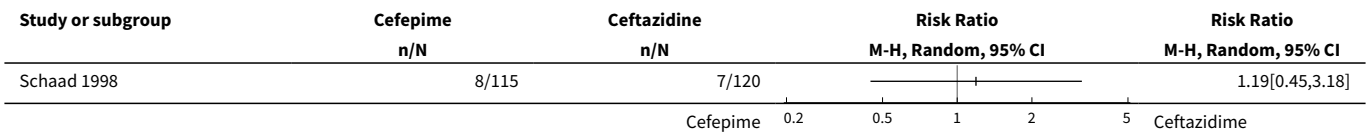
Analysis 6.1. Comparison 6 Cefepime versus ceftazidime, Outcome 1 Persistence or recurrence of initial pathogen.

Study or subgroup	Cefepime n/N	Ceftazidine n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
6.1.1 At end of IV therapy				
Schaad 1998	1/111	0/113		3.05[0.13,74.16]
6.1.2 At the end of IV and oral therapy				
Schaad 1998	0/96	4/102		0.12[0.01,2.16]
6.1.3 At 5-9 days after treatment				
Schaad 1998	5/96	2/91		2.37[0.47,11.91]

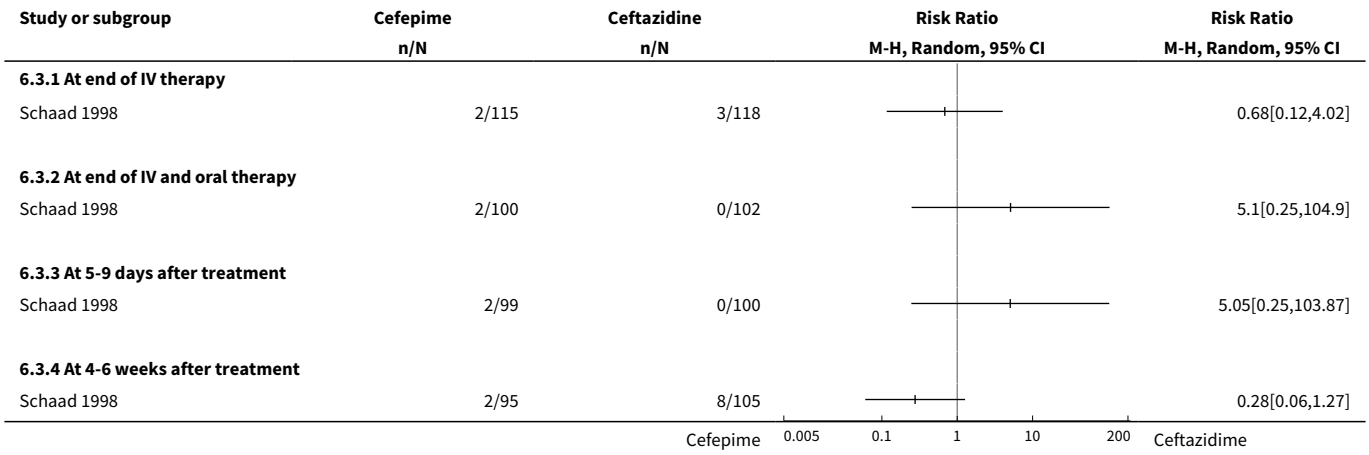




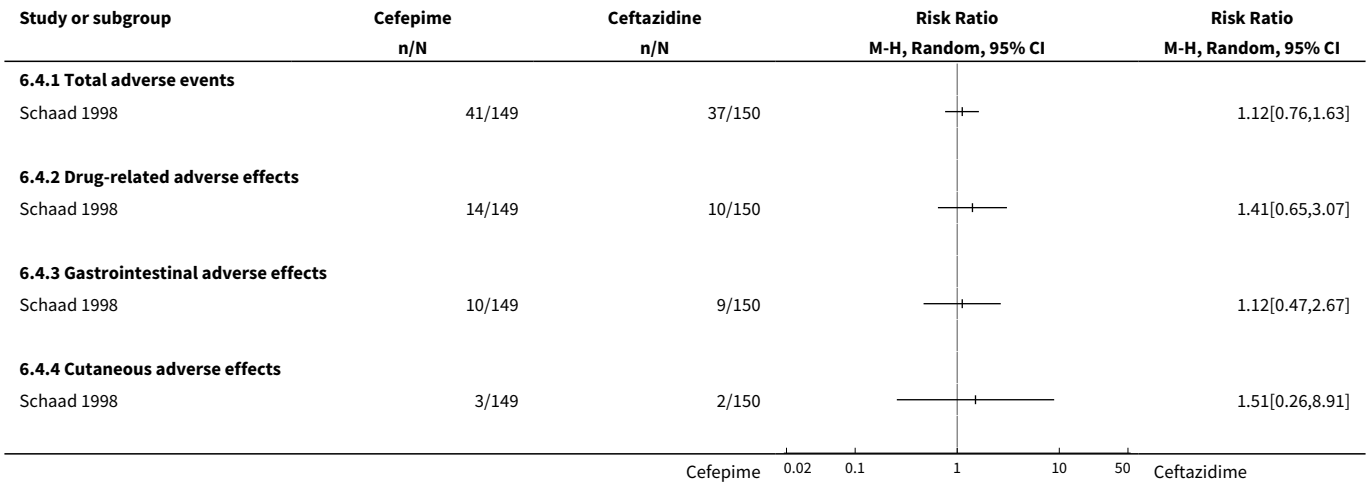
Analysis 6.2. Comparison 6 Cefepime versus ceftazidime, Outcome 2 Infection with new pathogen at 4-6 weeks.

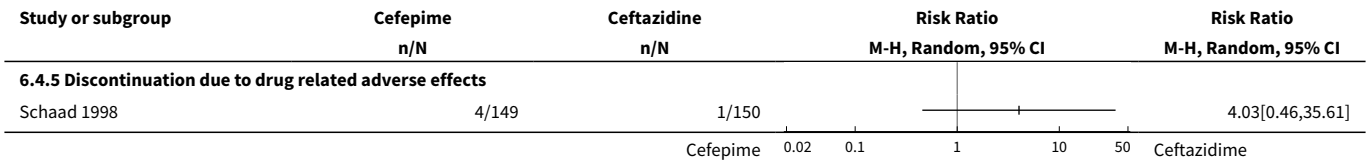


Analysis 6.3. Comparison 6 Cefepime versus ceftazidime, Outcome 3 Unsatisfactory clinical response.



Analysis 6.4. Comparison 6 Cefepime versus ceftazidime, Outcome 4 Adverse effects.



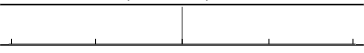


Comparison 7. Ceftriaxone versus cefotaxime

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent bacteriuria at 48 hours	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Bacteriuria 10 days after end of treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 All patients	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Normal renal tract imaging (post hoc analysis)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Abnormal renal tract imaging (post hoc analysis)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 UTI at 1 month after therapy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 All patients	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Normal renal tract imaging	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Abnormal renal tract imaging	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 All adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Skin eruptions	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Gastrointestinal adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 7.1. Comparison 7 Ceftriaxone versus cefotaxime, Outcome 1 Persistent bacteriuria at 48 hours.

Study or subgroup	Ceftriaxone n/N	Cefotaxime n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bakkaloglu 1996	0/50	0/50		Not estimable

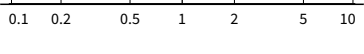


Analysis 7.2. Comparison 7 Ceftriaxone versus cefotaxime, Outcome 2 Bacteriuria 10 days after end of treatment.

Study or subgroup	Ceftriaxone n/N	Cefotaxime n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.2.1 All patients				
Bakkaloglu 1996	8/42	9/41		0.87[0.37,2.03]
7.2.2 Normal renal tract imaging (post hoc analysis)				
Bakkaloglu 1996	5/26	4/29		1.39[0.42,4.65]
7.2.3 Abnormal renal tract imaging (post hoc analysis)				
Bakkaloglu 1996	3/24	5/21		0.53[0.14,1.94]

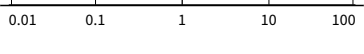
Analysis 7.3. Comparison 7 Ceftriaxone versus cefotaxime, Outcome 3 UTI at 1 month after therapy.

Study or subgroup	Ceftriaxone n/N	Cefotaxime n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.3.1 All patients				
Bakkaloglu 1996	8/42	11/39		0.68[0.3,1.5]
7.3.2 Normal renal tract imaging				
Bakkaloglu 1996	4/26	5/29		0.89[0.27,2.97]
7.3.3 Abnormal renal tract imaging				
Bakkaloglu 1996	4/24	6/21		0.58[0.19,1.79]



Analysis 7.4. Comparison 7 Ceftriaxone versus cefotaxime, Outcome 4 Adverse events.

Study or subgroup	Ceftriaxone n/N	Cefotaxime n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.4.1 All adverse events				
Bakkaloglu 1996	2/50	3/50		0.67[0.12,3.82]
7.4.2 Skin eruptions				
Bakkaloglu 1996	1/50	3/50		0.33[0.04,3.1]
7.4.3 Gastrointestinal adverse events				
Bakkaloglu 1996	1/50	0/50		3[0.13,71.92]

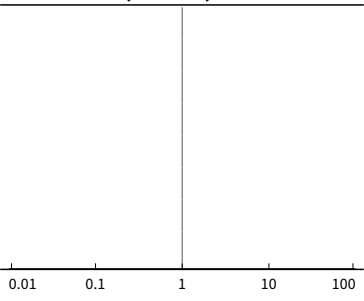


Comparison 8. Isepamicin versus amikacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent bacteriuria	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 After 2-3 days of therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 At 7 days after completing therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 At 30 days after completing therapy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 8.1. Comparison 8 Isepamicin versus amikacin, Outcome 1 Persistent bacteriuria.

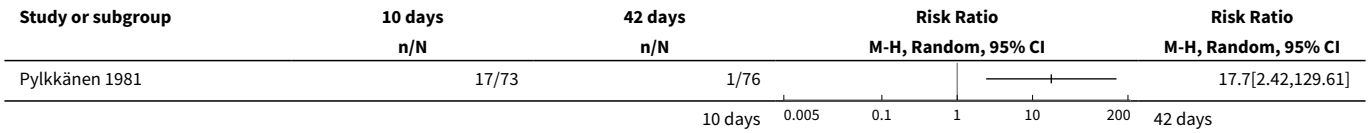
Study or subgroup	Isepamicin n/N	Amikacin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.1.1 After 2-3 days of therapy				
Kafetzis 2000	0/10	0/6		Not estimable
8.1.2 At 7 days after completing therapy				
Kafetzis 2000	0/10	0/6		Not estimable
8.1.3 At 30 days after completing therapy				
Kafetzis 2000	0/10	0/6		Not estimable



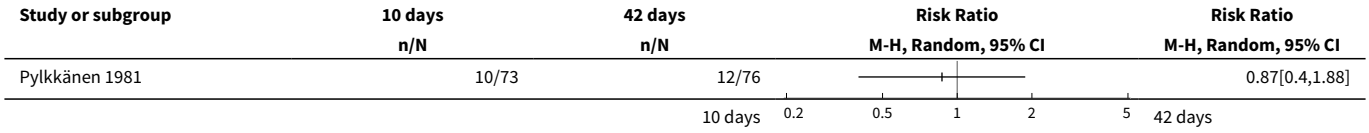
Comparison 9. 10 days versus 42 days of oral sulfafurazole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent UTI within 1 month after ceasing therapy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Recurrent UTI at 1-12 months after completing therapy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9 10 days versus 42 days of oral sulfafurazole, Outcome 1 Recurrent UTI within 1 month after ceasing therapy.



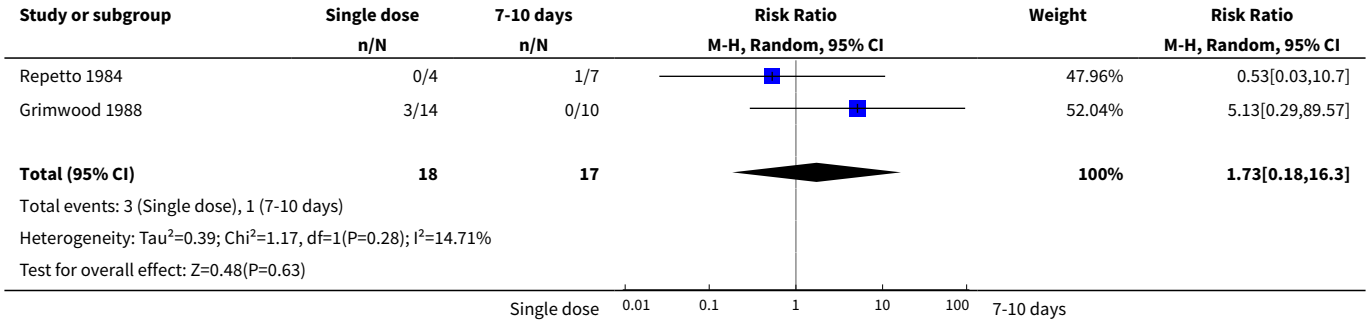
Analysis 9.2. Comparison 9 10 days versus 42 days of oral sulfafurazole, Outcome 2 Recurrent UTI at 1-12 months after completing therapy.



Comparison 10. Single dose of parenteral antibiotic versus 7-10 days oral therapy

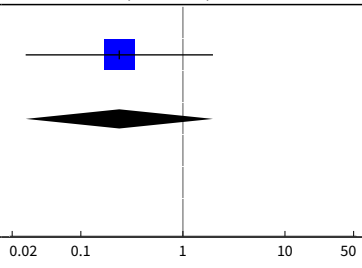
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent bacteriuria 1-2 days after treatment	2	35	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.18, 16.30]
2 UTI relapse or reinfection within 6 weeks	2	35	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.03, 1.97]

Analysis 10.1. Comparison 10 Single dose of parenteral antibiotic versus 7-10 days oral therapy, Outcome 1 Persistent bacteriuria 1-2 days after treatment.



Analysis 10.2. Comparison 10 Single dose of parenteral antibiotic versus 7-10 days oral therapy, Outcome 2 UTI relapse or reinfection within 6 weeks.

Study or subgroup	Single dose n/N	7-10 days n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Repetto 1984	0/4	0/7			Not estimable
Grimwood 1988	1/14	3/10		100%	0.24[0.03,1.97]
Total (95% CI)	**18**	**17**		**100%**	**0.24[0.03,1.97]**
Total events: 1 (Single dose), 3 (7-10 days)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.33(P=0.18)					

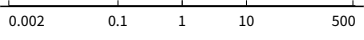


Comparison 11. 3 weeks versus 2 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistence/recurrence of bacteriuria	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Recurrence of clinical UTI	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

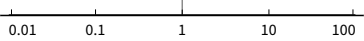
Analysis 11.1. Comparison 11 3 weeks versus 2 weeks, Outcome 1 Persistence/recurrence of bacteriuria.

Study or subgroup	3 weeks n/N	2 weeks n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Cheng 2006	0/39	7/41		0.07[0,1.19]



Analysis 11.2. Comparison 11 3 weeks versus 2 weeks, Outcome 2 Recurrence of clinical UTI.

Study or subgroup	3 weeks n/N	2 weeks n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Cheng 2006	0/39	2/41		0.21[0.01,4.24]



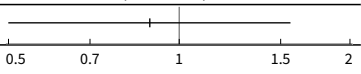
Comparison 12. Suppositories versus oral ampicillin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistence of clinical symptoms	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2 Persistence of bacteriuria	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

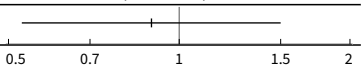
Analysis 12.1. Comparison 12 Suppositories versus oral ampicillin, Outcome 1 Persistence of clinical symptoms.

Study or subgroup	Suppositories n/N	Oral n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Fujii 1987	16/54	17/51		0.89[0.51,1.56]



Analysis 12.2. Comparison 12 Suppositories versus oral ampicillin, Outcome 2 Persistence of bacteriuria.

Study or subgroup	Suppositories n/N	Oral n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Fujii 1987	18/54	19/51		0.89[0.53,1.5]



ADDITIONAL TABLES

Table 1. Reported outcomes of included studies *(Continued)*

Study/ comparisons	Reported outcomes						
	Persistent bacteriuria at 48 to 72 hours	Bacteriuria at the end or ≥ 5 days of treatment	UTI at follow-up	Resolution of clinical symptoms	Symptomatic recurrence of UTI	Parenchymal renal damage on DSMA scan	Adverse effects
Oral therapy versus sequential short duration IV therapy and oral therapy							
Bocquet 2012				•		•	•
Hoberman 1999			•	•		•	
Montini 2007	•			•		•	•
Neuhaus 2008						•	•
Sequential short duration (3 to 4 days) IV therapy and oral therapy versus long duration (7to 14 days) IV therapy							
Benador 2001			•			•	
Bouissou 2008						•	
Francois 1997		•	•				•
Levtchenko 2001		•	•			•	
Noorbakhsh 2004		•					
Vilaichone 2001		•	•			•	•
Single dose parenteral therapy and oral therapy versus oral therapy alone							
Baker 2001	•		•	•			•
Different dosing regimens of aminoglycoside therapy							
Carapetis 2001	•			•			•
Chong 2003	•					•	•
Vigano 1992		•	•				•

Table 1. Reported outcomes of included studies *(Continued)*

Third generation cephalosporins versus other antibiotics						
Banfi 1993		•	•	•	•	•
Fischbach 1989	•		•	•		•
Marild 2009		•		•		•
Toporovski 1992		•	•			•
Third generation cephalosporins versus fourth generation cephalosporins						
Schaad 1998	•	•	•	•		•
Ceftriaxone versus cefotaxime						
Bakkaloglu 1996	•	•	•			•
Aminoglycosides versus aminoglycosides						
Kafetzis 2000		•	•			•
Different durations of the same oral antibiotic						
Pylkkänen 1981			•			
Single dose parenteral therapy versus oral therapy alone						
Grimwood 1988		•	•			
Repetto 1984		•	•			
Different durations of different antibiotics						
Cheng 2006		•			•	
Different routes of antibiotic administration						
Fujii 1987		•		•		
Three days versus 10 days of oral therapy						

Table 1. Reported outcomes of included studies *(Continued)*

Khan 1981	•

DMSA - Tc99m-dimercaptosuccinic acid nuclear scan; UTI - urinary tract infection

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	#1 PYELONEPHRITIS* explode all trees #2 pyelonephritis #3 URINARY TRACT INFECTIONS explode all trees #4 urinary next tract next infection* #5 kidney next infection* #6 #1 or #2 or #3 or #4 or #5 #7 CHILD explode all trees #8 #6 and #7 #9 ADULT explode all trees #10 #8 not #9
MEDLINE	1. pyelonephritis/ 2. urinary tract infections/ 3. UTI.tw. 4. urinary tract infection$.tw. 5. pyelonephritis.tw. 6. or/1-5 7. exp antibiotics/ 8. antibiotic treatment.tw. 9. antibiotic therap$.tw. 10. antibiotic$.tw. 11. or/7-10 12. 6 and 11 13. limit 12 to all child <0 to 18 years>
EMBASE	1. exp pyelonephritis/ 2. urinary tract infection/ 3. UTI.tw. 4. urinary tract infection$.tw. 5. pyelonephritis.tw. 6. or/1-5 7. exp antibiotic agent/ 8. antibiotic therapy/ 9. antibiotic treatment.tw. 10. antibiotic therap$.tw. 11. antibiotic$.tw. 12. or/7-11 13. 6 and 12 14. exp child/ 15. exp adolescent/ 16. 14 or 15 17. 13 and 16

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria

(Continued)

Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with

(Continued)

	substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
10 July 2014	New search has been performed	New search, new studies included
10 July 2014	New citation required and conclusions have changed	New studies included

HISTORY

Protocol first published: Issue 3, 2002
Review first published: Issue 3, 2003

Date	Event	Description
1 February 2010	Amended	Minor correction of data for Analysis 1.3.2 - no change in summary estimate of effect
13 May 2009	Amended	Contact details updated.
17 June 2008	Amended	Converted to new review format.

Date	Event	Description
20 October 2007	Amended	Full study data for Monitini 2003 added
14 August 2007	New citation required and conclusions have changed	Substantive amendment
5 February 2007	Amended	Five new studies added
15 October 2004	Amended	Two new studies added

CONTRIBUTIONS OF AUTHORS

Designing the review: PB, EH with Cochrane Renal Group guidelines
Coordinating the review; PB, EH
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Entering data into RevMan; PB, EH, YS
Analysis of data; PB, EH, YS
Interpretation of data: PB, EH, NW, YS, AW
Writing the review; PB, EH, NW, YS, AW
Providing general advice on the review; EH, JC, AW

DECLARATIONS OF INTEREST

Yvonne Strohmeier: nothing to declare
Elisabeth Hodson: nothing to declare
Narelle Willis: nothing to declare
Angela Webster: nothing to declare
Jonathan Craig: nothing to declare

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Risk of bias assessment has replaced the quality assessment checklist; methodology has been updated to be in line with current Cochrane Collaboration guidelines.

NOTES

Issue 3, 2010. Correction of data entered for Hoberman 1999 in Analysis 1.6.2 (Patients with kidney parenchymal damage on initial DMSA). Data published in Issue 4, 2007 were 17/100 for oral therapy and 12/87 for IV then oral therapy. The correct numbers are 15/100 for oral therapy and 11/87 for IV then oral therapy. There is no significant change in the summary estimate (Issue 4, 2007: RR 0.79, 95% CI 0.53 to 1.16; Issue 3, 2010: RR 0.77, 95% CI 0.53 to 1.11).

The authors wish to thank Dr Bodil Als-Nielsen for notifying us of this error.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Oral; Anti-Bacterial Agents [administration & dosage] [*therapeutic use]; Drug Therapy, Combination; Injections, Intravenous; Pyelonephritis [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Humans; Infant