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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 infection in infants. The most severe form of UTI is acute pyelonephritis, which results in significant acute morbidity and may cause permanent renal damage. Published guidelines recommend treatment of acute pyelonephritis initially with intravenous (IV) therapy followed by oral therapy for seven to 14 days though there is no consensus on the duration of either IV or oral therapy.

Objectives

To determine the benefits and harms of different antibiotic regimens for the treatment of acute pyelonephritis in children.

Search methods

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, reference lists of articles and abstracts from conference proceedings without language restriction.
Date of most recent search: June 2004.

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

Two reviewers independently assessed trial quality and extracted data. Statistical analyses were performed using the random effects model and the results expressed as relative risk (RR) for dichotomous outcomes or weight mean difference (WMD) for continuous data with 95% confidence intervals (CI).

Main results

Eighteen trials (2612 children) were eligible for inclusion. No significant differences were found in persistent renal damage at six months (one trial, 306 infants: RR 1.45, 95% CI 0.69 to 3.03) or in duration of fever (WMD 0.80, 95% CI -4.41 to - 6.01) between oral cefixime therapy (14 days) and IV therapy (three days) followed by oral therapy (10 days). Similarly no significant differences in persistent renal damage (three trials, 315 children: RR 0.99, 95% CI 0.72 to 1.37) were found between IV therapy (3-4 days) followed by oral therapy and IV therapy for 7-14 days. In addition no significant differences in efficacy were found between daily and thrice daily administration of aminoglycosides (one trial, 179 children, persistent symptoms at three days: RR 1.98, 95% CI 0.37 to 10.53).

Authors' conclusions

These results suggest that children with acute pyelonephritis can be treated effectively with oral cefixime or with short courses (2-4 days) of IV therapy followed by oral therapy. If IV therapy is chosen, single daily dosing with aminoglycosides is safe and effective. Trials are required to determine the optimal total duration of therapy and if other oral antibiotics can be used in the initial treatment of acute pyelonephritis.

PLAIN LANGUAGE SUMMARY

Oral antibiotics may be as effective as the combination of injection 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). It causes high fever, vomiting, stomach pain, irritability and poor feeding in infants. Usual treatment is antibiotics given first by injection (IV) and then orally for 7-14 days to clear the infection and prevent kidney damage. These results suggest that children with acute pyelonephritis can be treated effectively with oral cefixime or with short courses (2-4 days) of IV therapy followed by oral therapy. If IV therapy is chosen, single daily dosing with aminoglycosides is safe and effective.

BACKGROUND

The urinary tract is a common site of bacterial infection in infants and young children. Population based studies from Sweden demonstrate that 8% of girls and 2% of boys are diagnosed with at least one urinary tract infection (UTI) by the age of seven years (Hellstrom 1991). UTI is defined by the presence of bacteria within the urine (bacteriuria), which when cultured is measured in colony forming units/litre (cfu/L) of uncentrifuged urine. The diagnosis of UTI is generally confirmed by the pure growth of a bacteria from culture of an uncontaminated urine sample of greater than 10^8 cfu/L (Hellerstein 1982).

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

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 99^m labelled dimercaptosuccinic acid (DMSA) renal scan and markers of inflammation in the blood such as erythrocyte sedimentation rate and C-reactive protein.

Acute pyelonephritis is associated with significant short-term morbidity, including shock and septicaemia, especially in infants, and acute renal parenchymal injury. This acute injury has been demonstrated on DMSA renal scan in 20% to 90% of children shortly after diagnosis with UTI (Garin 1998). Permanent renal damage may occur following acute pyelonephritis and is more frequent in children who have multiple episodes (Smellie 1985). Serial DMSA renal scans of children after an episode of acute pyelonephritis show that about 40% of children with acute changes on DMSA scans have permanent renal damage at follow up (Jakobsson 1994; Stokland 1996). However the long term significance of renal damage following acute pyelonephritis in previously normal kidneys remains unclear.

A wide variety of antibiotic agents have been used to treat acute pyelonephritis in children (administered by oral and intravenous (IV) routes) without consensus on which are the most effective. Most authorities recommend commencing antibiotic therapy by parenteral route in infants and young children with suspected acute pyelonephritis (AAP 1999; RCP 1991), although a recent randomised control trial suggests that acute pyelonephritis can be treated with oral antibiotics (Hoberman 1999).

The aims of this systematic review are to assess the benefits and harms of the antibiotics used to treat acute pyelonephritis in children, to help determine the optimum antibiotic agent(s), route of administration and duration of treatment for this group.

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, in which antibiotics are used in the treatment of children (aged birth to 18 years) with acute pyelonephritis were included. Where studies included both patients with acute pyelonephritis and patients with cystitis, they were included if the data for the patients with acute pyelonephritis could be extracted separately, otherwise these studies were excluded. If more than one publication of a trial was identified, all publications were to be reviewed and the publication with the most complete data was to be included.

Types of participants

Inclusions
Children aged 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 (bacterial growth on urine culture of more than 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 trials. Children with previously diagnosed urinary tract abnormalities including vesicoureteric reflux (VUR) or previous UTI were included.

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

Types of interventions

1. Different antibiotic agents
2. IV antibiotic versus oral antibiotic
3. Different doses and/or duration of the same antibiotic
4. Antibiotic versus placebo, no therapy or alternative non-antibiotic therapy

Types of outcome measures

Short-term outcome measures

- Duration of fever
- Persistent symptoms
- Acute renal parenchymal damage on DMSA renal scan
- Length of hospital stay for in-patients
- 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)

Long-term outcome measures

- Renal damage (as defined by authors of included trials)
- Hypertension
- Chronic renal failure

Search methods for identification of studies

Relevant trials were obtained from the following sources without language restriction (see Additional Table 1 - *Electronic search strategies)*:

- Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Issue 2, 2004) and the Cochrane Renal Group's Specialised Register.
- MEDLINE using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Dickersin 1994) (see Renal Group Module) with a specific search strategy for acute pyelonephritis in children (1966 - June 2004)
- EMBASE using a search strategy adapted from that developed for the Cochrane Collaboration for the identification of randomised controlled clinical trials (Lefebvre 1996) (see Renal Group Module) together with a specific search strategy for acute pyelonephritis in children. (1980 to June 2004)
- Reference lists of nephrology textbooks, review articles and relevant trials.
- Reference lists of abstracts from nephrology and paediatric scientific meetings.
- Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous trials.

Data collection and analysis

Included and excluded studies

The review was undertaken by three reviewers (PB, EH and JC). The search strategy described was used to obtain titles and abstracts of studies that were considered relevant to the review. The titles and abstracts were independently screened by PB and EH, who discarded studies that were irrelevant, although studies and reviews that included relevant data or information on trials were retained initially.

Reviewers PB and EH independently assessed abstracts and, if necessary the full text, of these studies to determine which studies satisfied the inclusion criteria. Data extraction was carried out by the same reviewers independently using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Further information from the original author was obtained by written correspondence and any relevant information obtained in this manner was included in the review. Discrepancies were resolved in consultation with JC.

Study quality

The quality of studies to be included was assessed independently by PB and EH without blinding to authorship or journal of publication using the checklist developed for the Cochrane Renal Group. Discrepancies were resolved by consensus and when necessary by discussion with JC. The quality items assessed were allocation concealment, intention-to-treat analysis, completeness of follow-up and blinding of investigators, participants and outcome assessors (Hollis 1999; Juni 1999; Moher 1998; Schulz 1995).

Quality checklist

1. Allocation concealment

Adequate: Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study
Unclear: Randomisation stated but no information on method used is available
Inadequate: Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group

2. Blinding

Blinding of investigators: Yes/No/not stated
Blinding of participants: Yes/No/not stated
Blinding of outcome assessor: Yes/No/not stated
Blinding of data analysis: Yes/No/not stated
The above are considered not blinded if the treatment group could be identified in >20% of participants due to side effects of treatment or the treatment groups could be identified through different routes or frequency of administration of trial medications.

3. Intention-to-treat analysis

A. Yes: specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment
B. No: not reported and lack of intention-to-treat analysis confirmed on study assessment (patients who were randomised but were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation).
C. Not stated: not reported and could be determined (studies with 100% follow-up of patients included so that patient exclusion after randomisation cannot be excluded)

4. Completeness of follow-up

Percentage of participants lost to follow-up or with no data for the primary outcome of effectiveness.

Statistical assessment

Data was entered independently by both reviewers into RevMan 4.2. For dichotomous outcomes (persisting bacteriuria, recurrent UTI) results were expressed as relative risk (RR) with 95% confidence intervals (CI). Data were pooled using the random effects model but the fixed effects model was also used to ensure robustness of the model chosen and susceptibility to outliers. Where continuous scales of measurement were used to assess the effects of treatment (duration of fever), the weighted mean difference (WMD) was used. Heterogeneity was analysed using a Chi squared test on N-1 degrees of freedom with an alpha of 0.1 used for statistical significance.

Subgroup analysis was planned to explore possible sources of heterogeneity (participants, treatments and study quality). 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.

Insufficient RCTs comparing the same intervention were identified to examine for publication bias using a funnel plot (Egger 1997).

RESULTS

Description of studies

Of 1520 titles and abstracts identified, 51 were chosen for full text review. Eleven trials were excluded because data from children with acute pyelonephritis could not be excluded from those with lower UTI (9), paediatric data could not be separated from adult data (1) or immunomodulatory agents and not antibiotics were used (1). The remaining studies chosen for full text review either involved children with lower UTI only or were found not to be RCTs.
Sixteen parallel RCTs involving 1806 children fulfilled the eligibility criteria and were included in this systematic review. A further search from 2002-2004 identified two further trials (Chong 2003; Montini 2003-abstract only)

Trial participants

Trials recruited participants from the ages of rwo weeks and up to 15 years. Three trials did not specify the age range (Bakkaloglu 1996; Levtchenko 2001; Pylkkänen 1981).

- One trial excluded children with weights below 3 kg (Schaad 1998).
- One trial (Fischbach 1989) excluded children aged one year and below.
- Two trials (Bakkaloglu 1996; Toporovski 1992) excluded children younger than two years.
- One trial excluded children older than 24 months (Hoberman 1999).

Health care settings

- Five trials gave all trial treatments while patients were in hospital (Bakkaloglu 1996; Carapetis 2001; Chong 2003; Kafetzis 2000; Vigano 1992).
- In three trials children were treated as outpatients only (Baker 2001; Pylkkänen 1981; Repetto 1984).
- In the remaining ten trials children received treatment in both in- and outpatient settings (Benador 2001; Fischbach 1989; Francois 1997; Hoberman 1999; Grimwood 1988; Levtchenko 2001; Montini 2003; Schaad 1998; Toporovski 1992; Vilaichone 2001).

Urine collection

- In nine trials urine specimens were collected by suprapubic aspiration, catheter or mid stream specimens (Baker 2001; Carapetis 2001; Grimwood 1988; Hoberman 1999; Kafetzis 2000; Pylkkänen 1981; Repetto 1984; Toporovski 1992; Vigano 1992).
- Four trials also included specimens obtained by strap-on bag (Benador 2001; Levtchenko 2001; Schaad 1998; Vilaichone 2001).
- The method of urine collection was not specified in five trials (Bakkaloglu 1996; Chong 2003; Fischbach 1989; Francois 1997; Montini 2003).

Diagnosis

- In 15 included studies all participants had acute pyelonephritis.
- The remaining three studies enrolled children with both acute pyelonephritis and lower UTIs (Grimwood 1988; Pylkkänen 1981; Repetto 1984) and the data from children with acute pyelonephritis have been included in this review.

Definition of acute pyelonephritis

The criteria required for diagnosis of acute pyelonephritis in children with UTI varied between studies.

- Three trials required fever > 38ºC (Baker 2001; Hoberman 1999; Montini 2003), six required fever and at least one additional clinical feature (Bakkaloglu 1996; Carapetis 2001; Chong 2003; Grimwood 1988; Repetto 1984; Schaad 1998; Toporovski 1992).
- Six trials required fever, clinical features and laboratory abnormalities (C-reactive protein, erythrocyte sedimentation rate, white blood count) (Fischbach 1989; Francois 1997; Kafetzis 2000; Levtchenko 2001; Pylkkänen 1981; Vigano 1992).
- Two trials required fever, clinical features and acute renal parenchymal injury on DMSA scan (Benador 2001; Vilaichone 2001).

Exclusion criteria

Common reported exclusion criteria

- Impaired renal function (10 trials: Carapetis 2001; Chong 2003; Fischbach 1989; Francois 1997; Kafetzis 2000; Repetto 1984; Schaad 1998; Toporovski 1992; Vigano 1992; Vilaichone 2001).
- Known severe urinary tract abnormality (eight trials: Baker 2001; Benador 2001; Francois 1997; Hoberman 1999; Levtchenko 2001; Repetto 1984; Vigano 1992; Vilaichone 2001).
- Known sensitivity to trial medications (13 trials: Baker 2001; Benador 2001; Carapetis 2001; Chong 2003; Fischbach 1989; Francois 1997; Hoberman 1999; Kafetzis 2000; Repetto 1984; Schaad 1998; Toporovski 1992; Vigano 1992; Vilaichone 2001).

Other exclusion criteria

- Recent antibiotic use (five trials: Baker 2001; Chong 2003; Fischbach 1989; Kafetzis 2000; Vilaichone 2001).
- Previous UTI (four trials: Fischbach 1989; Francois 1997; Hoberman 1999; Vilaichone 2001).
- Clinical signs of shock at presentation (three trials: Baker 2001; Francois 1997; Hoberman 1999).
- Immune compromise (three trials: Carapetis 2001; Francois 1997; Schaad 1998).
- Known hearing impairment (Four trials: Carapetis 2001; Chong 2003; Kafetzis 2000; Vigano 1992).

Three trials did not specify any exclusion criteria (Bakkaloglu 1996; Grimwood 1988; Pylkkänen 1981).

Trial comparisons

Trials were grouped according to the aims of each trial.

- Two studies compared oral therapy with short duration IV therapy followed by oral therapy (comparison 01: Hoberman 1999; Montini 2003).
- In four studies short duration IV therapy (3 to 4 days) followed by oral therapy was compared with long duration IV therapy (7 to 14 days) (comparison 02:Benador 2001; Francois 1997; Levtchenko 2001; Vilaichone 2001).

- The addition of a single dose of parenteral antibiotic to oral therapy was compared to oral therapy alone in one study (comparison 03:Baker 2001).
- Three studies compared different dosing frequencies of the same antibiotic agents (comparison 04: Carapetis 2001; Chong 2003; Vigano 1992).

Five studies compared different antibiotics (comparisons 05, 06, 07, 08: Bakkaloglu 1996; Fischbach 1989; Kafetzis 2000; Schaad 1998; Toporovski 1992). One of these studies (Toporovski 1992) had two experimental groups using different doses of antibiotic. Since the treatment response did not differ, the experimental groups were combined.

- One study compared different durations of the same oral antibiotic (comparison 09: Pylkkänen 1981).
- Two studies assessed single dose parenteral therapy against 7 to 10 days of oral antibiotic therapy (comparison 10: Grimwood 1988; Repetto 1984).

Trial outcomes

- Persistent of bacteriuria at 48 to 72 hours (six trials: Baker 2001; Bakkaloglu 1996; Carapetis 2001;Chong 2003; Fischbach 1989; Schaad 1998) or at the end of treatment or after at least seven days of treatment (10 trials: Bakkaloglu 1996; Francois 1997; Grimwood 1988; Kafetzis 2000; Levtchenko 2001; Repetto 1984; Schaad 1998; Toporovski 1992; Vigano 1992; Vilaichone 2001) and UTI during follow-up (15 trials: Baker 2001; Bakkaloglu 1996; Benador 2001; Fischbach 1989; Francois 1997; Grimwood 1988; Hoberman 1999; Kafetzis 2000; Levtchenko 2001; Pylkkänen 1981; Repetto 1984; Schaad 1998; Toporovski 1992; Vigano 1992; Vilaichone 2001) were the most commonly reported outcomes.
- Resolution of clinical symptoms was reported in six trials (Baker 2001; Carapetis 2001; Fischbach 1989; Hoberman 1999; Montini 2003; Schaad 1998).
- Parenchymal renal damage on DMSA scan was reported in five trials (Benador 2001; Chong 2003; Hoberman 1999; Levtchenko 2001; Vilaichone 2001).
- Adverse effects were reported in 11 trials (Baker 2001; Bakkaloglu 1996; Carapetis 2001; Chong 2003; Fischbach 1989; Francois 1997; Kafetzis 2000; Schaad 1998; Toporovski 1992; Vigano 1992; Vilaichone 2001).

Risk of bias in included studies

There were 2612 children with acute pyelonephritis enrolled in the 18 included trials (see Additional Table 2 -*Methodological quality of included studies*). Of these children 2320 (89%) were assessed for at least one outcome of effectiveness. In two trials (Francois 1997; Schaad 1998) 87% and 79% respectively of participants were evaluated for efficacy while all were analysed for adverse effects. In three trials (Grimwood 1988; Pylkkänen 1981; Repetto 1984) patients were identified post randomisation as having acute pyelonephritis or cystitis; only patients with acute pyelonephritis are included in the review.

Allocation concealment

Allocation was adequately concealed in six trials (Baker 2001; Benador 2001; Carapetis 2001; Francois 1997; Hoberman 1999; Schaad 1998); in the remaining trials it was unclear as to whether allocation was concealed.

Blinding

Absence of blinding of participants or investigators was reported or detected in 17 trials, however in one trial (Kafetzis 2000) it was unclear whether there was blinding. One trial (Bakkaloglu 1996) was reported to be double-blinded but antibiotics were administered at different frequencies and no placebos were given. Blinding of assessment of one or more outcomes was reported in six trials (Baker 2001; Benador 2001; Carapetis 2001; Hoberman 1999; Levtchenko 2001; Schaad 1998); there was no comment on blinding of outcome assessment in the remaining trials. Three (Benador 2001; Hoberman 1999; Levtchenko 2001) of the four trials, in which the presence or absence of persistent renal damage on DMSA scan at three to six months was the primary outcome, reported that the scan results were reported by investigators, who were unaware of the child's treatment assignment. No trial was stratified for the presence or absence of VUR; post hoc subgroup analyses of patients with and without VUR were reported in two trials (Benador 2001; Hoberman 1999).

Intention-to-treat

In two trials data were analysed on an intention-to-treat basis (Carapetis 2001; Hoberman 1999).

Completeness of follow-up

In five trials loss-to follow up of patients varied between 0.3% and 6% (Baker 2001; Benador 2001; Hoberman 1999; Levtchenko 2001; Schaad 1998); in the remaining trials all included patients completed follow-up.

Effects of interventions

As the results from random and fixed effects models did not differ, only results from the random effects model are reported. Few trials were available for combination in meta-analyses. Among the limited meta-analyses no significant heterogeneity was detected. No pre-planned subgroup analyses for outcomes according to patient age (infant, child, adolescent) were possible from the data available. Post hoc subgroup analyses were possible for age (less than or greater than one year, Benador 2001) and VUR (Benador 2001; Hoberman 1999).

Oral therapy verus IV therapy (comparison 01)

Two trials (Hoberman 1999; Montini 2003) involving 693 children compared oral antibiotics (cefixime or amoxycillin/clavulinic acid) for 10 to 14 days with IV ceftriaxone for three days or defervescence followed by oral antibiotics to complete the course of therapy.

- Time to resolution of fever did not differ significantly between groups (outcome 01, two trials: WMD 1.54, 95% CI -1.67 to 4.76). Time to fever resolution was the only outcome reported in one trial available in abstract only (Montini 2003).
- There was no significant difference between groups in the rate of symptomatic UTI recurrences within six months (outcome 02.02: RR 0.67, 95% CI 0.27 to 1.67).
- There were no significant differences in the rate (outcome 03: RR 1.45, 95% CI 0.63 to 3.03) or size (outcome 04: RR -0.70, 95% CI -1.74 to 0.34) of persistent renal parenchymal defects on DMSA scan at six months.
- Post hoc subgroup analysis (outcomes 05.02, 05.03) found no difference in the number of renal parenchymal defects on DMSA scan at six months between children with VUR (RR 1.88, 95% CI 0.83 to 4.24) and those without VUR (RR 0.80, 95% CI 0.23 to 2.73). However post hoc analysis (outcome 05.05) raised the

possibility that among children with VUR (grade III-V), persistent renal parenchymal defects on DMSA scan at six months occurred more frequently after oral than IV therapy.
- The average cost of treatment for each patient was US$3630 and US$7382 for the oral and IV groups respectively.

Short duration versus long duration IV therapy (comparison 02)
Four trials (Benador 2001; Francois 1997; Levtchenko 2001; Vilaichone 2001) involving 480 children compared oral with IV administration after an initial 3 to 4 days of IV therapy for both groups.

- Two trials compared IV ceftriaxone (3 to 4 days) followed by oral cefixime (Benador 2001) or ceftibuten (Vilaichone 2001) with IV ceftriaxone (10 days).
- One trial (Levtchenko 2001) compared IV temocillin (three days) followed by oral amoxicillin or amoxicillin/clavulanic acid with IV temocillin (seven days).
- The fourth trial (Francois 1997) compared IV cefotaxime (four days) followed by oral amoxycillin/clavulanic acid with IV cefotaxime (14 days).
- Two of these trials (Benador 2001; Levtchenko 2001) also converted the IV group to oral therapy after 7 to 10 days to complete 15 to 21 days of treatment.
- Persistent bacteriuria at the end of treatment was reported in only one patient in the three trials in which this outcome was reported (outcome 01).
- There was no significant difference between the two groups for recurrent UTI within 6 to 12 months (outcome 02, four trials: RR 1.15, 95% CI 0.52 to 2.51)
- The number of persisting renal parenchymal defects seen on DMSA scan at 3 to 6 months did not differ significantly (outcome 03, three trials: RR 0.99, 95% CI 0.72 to 1.37).
- Post hoc subgroup analysis (outcome 04: Benador 2001; Vilaichone 2001) showed that the number of children with persisting renal parenchymal defects on DMSA scan did not differ between those with VUR (two trials: RR 0.99, 95% CI 0.56 to 1.74) and without VUR (two trials: RR 1.19, 95% CI 0.81 to 1.76) and those aged under one year (one trial: RR 1.46, 95% CI 0.71 to 3.01) and one year and over (one trial: RR 0.89, 95%CI 0.59 to 1.34).
- The only adverse effects reported were gastrointestinal upsets and the frequency of these did not differ between therapy routes (outcome 05, two studies: RR 1.29, 95% CI 0.55 to 3.05).
- 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 176-896) compared with 3545 French Francs (range 2478-4673) for 10 days of IV therapy (Francois 1997).

Single dose parenteral therapy and oral treatment versus oral therapy alone (comparison 03)
One trial (Baker 2001) involving 69 children compared the addition of a single intramuscular dose of the third generation cephalosporin, ceftriaxone, to an oral course of trimethoprim with sulphamethoxazole. There was no significant difference in:

- persistence of bacteriuria after 48 hours (outcome 01: RR 0.77, 95% CI 0.19 to 3.20),
- persistence of clinical symptoms (outcome 02: RR 0.82, 95% CI 0.24 to 2.81), or
- total adverse events (outcome 04: RR 1.37, 95% CI 0.33 to 5.68) between groups.
- No child developed a symptomatic UTI during one month (outcome 03) after treatment.

Different dosing regimens of aminoglycoside therapy (comparison 04)
Three trials involving 495 children compared daily parenteral administration of gentamicin (Carapetis 2001; Chong 2003) or netilmicin (Vigano 1992) to eight-hourly administration of the aminoglycosides.

- There was no significant difference in the risk for persisting bacteriuria 1 to 3 days after commencing treatment with either dose frequency (outcome 01, three trials: RR 1.98, 95% CI 0.37 to 10.53).
- There was no difference in the number of children with persisting clinical symptoms after three days of gentamicin (outcome 02: RR 1.98, 95%CI 0.37 to 10.53).
- Persisting bacteriuria one week after (outcome 03: RR 2.48, 95%CI 0.12 to 68.58) and recurrent UTI within one month (outcome 04: RR 1.18, 95%CI 0.33 to 4.23) after completing netilmicin treatment did not differ between treatment groups.
- The mean time to resolution of fever with gentamicin did not differ between groups in one trial (Chong 2003) (outcome 07: WMD 2.40, 95% CI -7.92 to 12.72). Median time to defervescence 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 trial (Carapetis 2001).
- There was no evidence that the number of children with hearing impairment (outcome 05, three trials: RR 2.83, 95% CI 0.33 to 24.56) and renal dysfunction (outcome 06, three trials: RR 0.75, 95% CI 0.20 to 2.82)

Different antibiotic agents (comparisons 05-08)
Five trials compared different antibiotics.

Comparison 05: In two trials involving 57 children treatment with IV cefotaxime (Fischbach 1989) or oral cefetamet (Toporovski 1992) was compared to amoxycillin/clavulanic acid.

- Two children treated with cefotaxime had persistent bacteriuria at 48 hours (outcome 01, two trials: RR 5.50, 95% CI 0.30 to 101.28).
- No child had recurrent UTI at 7 to 10 days after treatment (outcome 02, one trial) or persistent clinical symptoms at 7 to 10 days (outcome 03, one trial).
- Two children treated with cefotaxime had persistent fever for > 48 hours (outcome 04, one trial: RR 5.00, 95% CI 0.27 to 92.63).
- Gastrointestinal adverse effects were reported in three children treated with amoxycillin/clavulanic acid and three treated with cefetamet (outcome 05, two trials: RR 0.66, 95% CI 0.03 to 13.52).

Comparison 06: In one trial involving 299 children (Schaad 1998) IV cefipime (a fourth generation cephalosporin) was compared to IV ceftazidime (a third generation cephalosporin).

- No significant differences between groups were detected in the number of children with persistent or recurrent bacteriuria with the same pathogen at different time points after therapy

(outcome 01 - at end of IV and oral therapy: RR 0.12, 95% CI 0.01 to 2.16).

- Recurrent UTI with a different pathogenic organism at 4 to 6 weeks did not differ between groups (outcome 02: RR 0.68, 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 (outcome 03 - end of IV therapy: RR 0.68, 95% CI 0.12 to 4.02).
- The frequency of adverse effects did not differ between treatment groups (outcome 04 - drug related adverse effects: RR 1.41, 95% CI 0.65 to 3.07).

Comparison 07: In one trial involving 100 children (Bakkaloglu 1996) ceftriaxone was compared to cefotaxime in children aged over 24 months.

- No child had persistent bacteriuria at 48 hours (outcome 01).
- There were no significant differences between groups for bacteriuria at the end of treatment (outcome 02: RR 0.87, 95% CI 0.37 to 2.03), for recurrent infection at one month after therapy (outcome 03: RR 0.68, 95% CI 0.30 to 1.50), or for total adverse events (outcome 04: RR 0.67, 95% CI 0.12 to 3.82).
- Post hoc subgroup analysis (outcomes 02, 03) 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.

Comparison 08: In one trial involving 16 children (Kafetzis 2000) the aminoglycosides isepamicin and amikacin were compared.

- No patient in either group had persistence of bacteriuria after 48 hours of treatment, or seven days or 30 days after treatment (outcome 01).
- The 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 (comparisons 09-10)
Three trials compared different durations of antibiotic administration.

Comparison 09: One trial involving 149 children (Pylkkänen 1981) compared 10 days with 42 days of oral sulfafurazole.

- 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 (outcome 01: RR 17.70, 95% CI 2.42 to 129.61, P = 0.005).
- The number of children with recurrent UTI from 1 to 12 months after ceasing therapy did not differ between groups (outcome 02: RR 0.87, 95% CI 0.40 to 1.88).

Comparison 10: Two trials involving 61 children (Grimwood 1988; Repetto 1984) compared single dose parenteral antibiotic therapy with 7 to 10 days of oral therapy.

- There were no significant differences in the number of children with persistent bacteriuria after treatment (outcome 01, two trials: RR 1.73, 95% CI 0.18 to 16.30) or with recurrent UTI within six weeks (outcome 02, two trials: RR 0.24, 95% CI 0.03 to 1.97).

DISCUSSION

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 trials addressing the same or similar comparisons to allow assessment in meta-analyses. No trial specifically addressed whether the efficacy of therapies differed according to patient age. The sixteen included RCTs addressed a variety of different questions related to the therapy of children with acute pyelonephritis.

Oral therapy versus IV therapy
A single, adequately powered and well designed trial (Hoberman 1999), compared an oral third generation cephalosporin (cefixime) given for 14 days with IV therapy given for three days followed by oral therapy for 10 days in infants with acute pyelonephritis. This study found:

- The number of children with renal parenchymal damage on DMSA scan at follow-up did not differ significantly between groups though wide confidence intervals indicate residual imprecision (RR 1.45, 95% CI 0.69 to 3.03).
- The wide confidence intervals indicate that children treated with oral antibiotics could be 30% less likely or three times more likely to suffer renal damage on DMSA scan at six months post-UTI compared with children treated with IV antibiotics followed by oral therapy.
- Post hoc subgroup analysis found no significant differences in efficacy between children with or without VUR. However an analysis involving small numbers of children suggested the hypothesis that children with dilating VUR (grades III - V) were more likely to have renal damage on DMSA at six months post-UTI following oral treatment compared with IV followed by oral treatment.

Therefore uncertainty remains as to whether infants with acute pyelonephritis should be treated with oral antibiotics. Further data from a second trial (Montini 2003) are awaited to confirm the efficacy of oral antibiotics as initial therapy for children with acute pyelonephritis. In addition further data are required to determine whether treatment efficacy differs in children with dilating VUR compared with those without VUR or with undilating VUR.

Short duration versus long duration IV therapy
A meta-analysis of four trials (Benador 2001; Francois 1997; Levtchenko 2001; Vilaichone 2001) 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 renal parenchymal injury on DMSA scan at three to six months after UTI therapy did not differ significantly between treatment groups overall (RR 0.99, 95% CI 0.72 to 1.37) or in post hoc analysis of subgroups with VUR or without VUR or age under or over one year.

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. These data support published recommendations (Hellerstein 1995) and guidelines (AAP 1999;

RCP 1991) for the treatment of childhood UTI, which recommend parenteral antibiotics for the initial treatment of children with acute pyelonephritis. This is due to concerns about the increased risk of bacteraemia and renal damage if oral medication is not tolerated or not administered. The optimum duration of IV therapy is unknown as shorter courses of IV therapy (one to two days) have not been examined in RCTs.

Optimal duration of treatment

The optimal total duration of therapy for children with acute pyelonephritis remains unknown. Published recommendations suggest that treatment should be administered for seven to 14 days (AAP 1999; Hellerstein 1995). No trials were identified which compared different durations of therapy other than single dose therapy, however one trial (Pylkkänen 1981) compared 10 days with 42 days treatment for UTI. Such long duration therapy resulted in fewer UTI in the first month after ceasing therapy but there was no difference in the number of UTI between treatment durations after one month. The effect of long duration therapy may result from preventing re-infections with the original pathogen.

In two trials (Grimwood 1988; Repetto 1984) no differences were demonstrated in the number of children with persistent bacteriuria or recurrent UTI between single dose and standard (seven to 10 days) duration antibiotic treatment. No eligible studies were identified which compared short course (one to four days) with standard duration therapy for children with acute pyelonephritis. Included studies had small numbers of patients with few events and consequently wide confidence intervals indicating imprecision in the results. Systematic reviews (Keren 2002; Michael 2002; Tran 2001) comparing single dose or short course therapy with standard duration therapy for children with lower tract UTI have shown that short course is as effective as standard duration therapy in curing UTI but that single dose therapy is less effective. Currently there are insufficient trial data available to justify single dose therapy for children with acute pyelonephritis.

Single daily dosing with aminoglycosides

If IV therapy is to be used, three trials (Carapetis 2001; Chong 2003; Vigano 1992) 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 (Barza 1996). These findings have now been confirmed in children, in whom aminoglycoside pharmacokinetics and toxicity differ (Carapetis 2001), justifying the increasing use of daily aminoglycoside administration.

Efficacy of different antibiotics

The five trials (Bakkaloglu 1996; Fischbach 1989; Kafetzis 2000; Schaad 1998; Toporovski 1992) which compared different antibiotics did not demonstrate any advantage of one agent over another. One study (Baker 2001) demonstrated that a single dose of parenteral medication added to oral therapy did not improve efficacy compared with oral therapy alone. The antibiotics studied (predominantly third and fourth generation cephalosporin antibiotics) are costly and are not available in many countries, limiting the applicability of study results. Parenteral or oral cephalosporins, aminoglycosides, amoxycillin/clavulanic acid and trimethoprim/sulphamethoxazole are the most commonly recommended (AAP 1999; RCP 1991) and used (Cornu 1994; Levtchenko 2001a) agents for the treatment of children with acute pyelonephritis. Two small studies (Fischbach 1989; Toporovski 1992) compared a cephalosporin with amoxycillin/clavulanic acid. However no trial was identified which compared widely available and commonly used oral antibiotics (amoxycillin/clavulanic acid, trimethoprim/sulphamethoxazole, cephalexin). Similarly no trial was identified which compared the commonly used initial IV therapies of a third generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime) with gentamicin alone or combined with another antibiotic.

Adverse events

Adverse events resulting from antibiotics were reported in 10 trials. Events were uncommon and rarely resulted in treatment discontinuation or significant alteration. RCTs are generally not powered to detect significant side effects so that the low reported incidence of adverse events may not be generalisable to larger groups of children.

Methodological quality of trials

The quality of the included trials was quite variable, with the larger and more recent trials generally having adequate allocation concealment and blinding of outcome assessors. Intention-to-treat analysis was identified in only two trials. These quality factors were not present or not reported in most of the included trials. Absence of allocation concealment, blinding and intention-to-treat analysis may lead to over estimation of treatment effect and bias the results of the original studies and therefore the results of a systematic review (Hollis 1999; Juni 1999; Moher 1998; Schulz 1995). Publication bias resulting from the exclusion of some unpublished trials cannot be completely excluded. Formal testing for publication bias using funnel plots (Egger 1997) was not possible due to the small number of trials evaluating each intervention.

Other outcomes

Most trials excluded patients with major uropathology such as posterior urethral valves or neurogenic bladder so that study results cannot necessarily be applied to such children. Similarly, the trials were not stratified for the presence of dilating VUR, a risk factor for renal damage and further infection (Panaretto 1999). For clinicians treating children the most valuable outcomes relate directly to patient quality of life such as length of time to resolution of fever, duration of hospitalisation, recurrent symptomatic UTI and possible long-term sequelae including hypertension and chronic renal failure. The included studies predominantly examined bacteriological outcomes rather than clinical outcomes as measures of treatment efficacy. Only one study (Vilaichone 2001) reported on length of hospitalisation. No study was designed to study the development of longer-term sequelae other than parenchymal injury on DMSA scan. The cost of treatment is important information for health care services and was only provided in two trials (Francois 1997; Hoberman 1999).

AUTHORS' CONCLUSIONS

Implications for practice

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

- There are no significant differences in efficacy between treatment with an oral third generation cephalosporin (cefixime) given for 14 days and IV therapy given for three days followed by oral therapy for a total duration of 14 days. However wide

confidence intervals indicate residual imprecision. A confirming study showing that oral cefixime may be used initially for acute pyelonephritis in place of IV therapy is warranted. No data are available as to whether oral antibiotics other than cefixime are as effective as IV antibiotics in initial treatment. Further trials in which other commonly used oral antibiotics are compared with parenteral therapy are required.

- There are no significant differences in efficacy between IV antibiotic therapy given for three to four days followed by oral therapy with total therapy duration of 10 to 21 days and IV antibiotic therapy given for seven to 10 days with total duration of therapy of 10 to 21 days. The optimal duration of initial IV antibiotic therapy is unknown.
- Adequate data from RCTs are not available to determine the optimal total duration of antibiotic therapy required for acute pyelonephritis.
- Adequate data are not available to determine the efficacies of other widely used oral antibiotics (e.g. cephalexin, amoxycillin/clavulanic acid) in children with acute pyelonephritis either as initial therapy or after IV therapy in comparison with IV therapy.
- Single daily dosing of aminoglycosides is safe and effective compared with eight-hourly dosing.
- No data are available as to whether aminoglycosides alone or in combination are as effective as other medications including third generation cephalosporins in initial parenteral treatment.

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.
- Other commonly used oral antibiotics compared with short duration parenteral therapy followed by oral therapy.
- Initial treatment with oral antibiotics compared with parenteral therapy in children with dilating VUR or other major urinary tract malformation.

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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	Country: USA Tertiary hospital ED Randomisation method: NS

Baker 2001 *(Continued)*

	Power analysis: NS
Participants	Age: 6 mo -12 y Group 1: 34 (30F); mean age 3.6 y Group 2: 35 (32F); mean age 3.8 y Samples: MSU or catheter Exclusions: Patients with known uropathy; current antibiotic therapy; allergy to trial antibiotics; clinically unstable patients
Interventions	Group 1: Ceftriazone 50 mg/kg IM single dose, TMP/SMX 5 mg/kg/d (TMX) twice daily for 10 days Group 2: TMP/SMX in same dose only
Outcomes	1. Urine culture at 48 hous 2. Admission need at 48 hous 3. UTI &/or admission at 1 month 4. Adverse effects
Notes	Definition of APN: UTI & fever > 38C. Duration: 1 month

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Bakkaloglu 1996

Methods	Country: Turkey. Tertiary centre IP Randomisation method: NS Power analysis: NS
Participants	Age >/= 2 y Group 1: 50 (38F); age 8.1 (3.6SD) y; uropathy in 24 Group 2: 50 (40F); age 8.3 (2.9SD) y; uropathy in 21 Sample collection: NS Exclusions: NS
Interventions	Group 1: Ceftriaxone IV 50 mg/kg - daily for 10 days Group 2: Cefotaxime IV 50 mg/kg - dose twice daily for 10 days
Outcomes	1. Persistent bacteriuria at 2-3 days 2. Persistent bacteriuria at 10 days 3. Recurrent UTI within 4-5 weeks 4. Adverse events
Notes	Definition of APN: UTI & 2 + of fever, flank pain, pyuria, bacteriuria Duration: 1 month

Risk of bias

Bias	Authors' judgement	Support for judgement

Bakkaloglu 1996 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Benador 2001

Methods	Country: Switzerland. Multicentre tertiary hospital IP Randomisation: Blocks of 20 sealed opaque envelopes with equal numbers of treatment assignments; stratified by centre Power analysis: 106 per group to detect difference in rate of renal scarring of 20%
Participants	Age: 3 mo to 16 y Group 1: 118 (88F); age 1.0 y median (0.5-3.3 interquartile range). Uropathy found in 44 (VUR 40) Group 2: 111 (89F); age 2.4 y median (0.8-5.6 interquartile range). Uropathy found in 42 (VUR 36) Urine samples: Bag, MSU, SPA Exclusions: allergy to cephalosporins, known uropathology
Interventions	Group 1: Ceftriaxone IV 50 mg/kg daily for 3 days, then cefixime 4mg/kg/dose; 2 doses/d; 12 days. Total 15 days Group 2: Ceftriaxone as above for 10 days, then cefixime as above for 5 days. Total 15 days
Outcomes	1. Scarring on DMSA at 3 months 2. Recurrent UTI at 3 months
Notes	Definition of APN: UTI & Acute focal lesions on DMSA in patients with fever > 38C, flank pain, constitutional symptoms, C-reactive protein >10mg/L Duration: 3 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Carapetis 2001

Methods	Country: Australia Tertiary centre IP Randomisation: Block Power analysis: 87 per group to show 1 day difference in fever duration
Participants	Age: 1 mo to 12 y Group 1: 90 (63F); age 1 y median (0.4-6.0 range). Known uropathy 24; VUR detected in 22 Group 2: 89 (59F); age 1 y median (0.4-4.6 range). Known uropathy 19; VUR detected in 26 Samples: MSU, catheter, SPA Exclusions: Allergy to aminoglycoside; renal, hearing, vestibular dysfunction, neutropenia/immunodeficiency
Interventions	Group 1: Gentamicin IV daily - < 5 y 7.5 mg/kg/d; 5-10 y, 6mg/kg/d; > 10 y 4.5 mg/kg/d for 3.0 days (range 2 to 4)

Carapetis 2001 *(Continued)*

	Group 2: Gentamicin in same total dose each day but given in three divided doses for 2.7 days (range 2 to 3.3)
Outcomes	1. Resolution of clinical problem 2. Infective or non infective sequelae 3. Persistent bacteriuria at end of gentamicin 4. Adverse effects
Notes	Definition of APN: UTI & fever, vomiting, inability to take oral therapy Duration: 2 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Chong 2003

Methods	Country: Singapore Tertiary centre IP Randomisation: not stated. 220 to show 10% diff in UTI cure with 80% power
Participants	Age: I mo to 13 y 210 entered; 172 analysed Exclusions: No UTI 23, protocol violation 10, abnormal baseline otoacoustic emission (OAE) hearing test Group 1: 84 (40F), 0.95 (1.25SD) y, VUR 21 (11 no MCU) Group 2: 88 (47F), 0.90 (1.36SD) y, VUR 21 (15 no MCU) Urine: UTI confirmed on 2 clean catch urines (single organism >100,000/mL) or 1 catheter specimen (single organism >1000/mL) Exclusions: Known obstructive uropathy, aminoglycoside or other nephrotoxic agent in previous mth, allergy to aminoglycoside, renal or hearing impairment (including abnormal baseline OAE)
Interventions	Group 1: Gentamicin 5 mg/kg/d IV daily till defervescence (3.7 (1.8SD) d) Group 2: Gentamicin 6 mg/kg/d IV 8 hourly till defervescence (3.5 (1.8SD) d)
Outcomes	1. Negative urine culture at end of gentamicin 2. Time to defervescence 3. Nephrotoxicity (increase in creatinine by 50% or more) 4. Ototoxicity (loss of 30dB or more on repeat OAE test and confirmed on brain auditory evoked response (BAER) 5. Renal scars on DMSA scan at 3 months
Notes	Definition of UTI: Fever > 38C, pyuria>200/mL or offensive urine, dysuria, frequency, loin pain Duration 3 months

Risk of bias

Bias	Authors' judgement	Support for judgement

Chong 2003 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Fischbach 1989

Methods	Country: France Tertiary centre IP Randomisation: Number table Power analysis: NS
Participants	Age: >1 y Group 1: 10 (7F); known uropathy 1. Group 2: 10 (8F); known uropathy 1. Age < 1 y; 12 aged </=6 y. Sample collection: NS Exclusions: allergy to B-lactam antibiotics, UTI post operatively, antibiotics in previous 72 h, creatinine > 0.2 mmol/L
Interventions	Group 1: Cefotaxime IV 25 mg/kg/dose; 4 doses/d; 14 days Group 2: Amox/clav IV 25 mg/kg/dose; 4 doses/d; 7 d. Then amox/clav oral 50 mg/kg/d for 7 days. Total duration 14 days
Outcomes	1. Time to fever resolution 2. Persistent bacteriuria at 48-72 hours. 3. Recurrent UTI at 7 days after completing therapy
Notes	Definition of APN: UTI & fever > 38.5C, loin pain, poor clinical condition, elevated CRP, ESR Duration: 21 days

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Francois 1997

Methods	Country: France Multicentre tertiary centres IP Randomisation: Computer generated Power analysis: NS
Participants	Age: 0.5 to 10 y Group 1: 70 (64F); age 3.9 (2.9SD) y; VUR 26 Group 2: 77 (69F); age 4.3 (2.7SD) y; VUR 25 Sample collection: NS Exclusions: Previous APN, organisms resistant to trial antibiotics, allergy to cephalosporins, B-lactams, aminoglycosides, known uropathology, need for IV antibiotics based on ultrasound, renal failure, immune deficiency, other infection
Interventions	Group 1: Ceftriaxone IV 50 mg/kg/d, daily dose & netilmicin IV 6-7.5 mg/kg/d in 3 divided doses for 4 days. Then oral cefixime 4 mg/kg/dose; 2 doses/d; 6 days

Francois 1997 *(Continued)*

	Group 2: Ceftriaxone & netilmicin as group 1 for 4 days then ceftriaxone IV 50 mg/kg/day as single dose; 6 days
Outcomes	1. Persistent bacteriuria 2 days after end of therapy 2. Recurrent UTI in 20 days after therapy 3. Adverse events
Notes	Definition of APN: UTI & fever > 38C, pyuria, CRP increased Duration: 1 month

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Grimwood 1988

Methods	Country: New Zealand Tertiary centre IP & OPD Randomisation: Number table; Not stratified for APN Power analysis: NS
Participants	Age: 2 wk to 12 y Group 1: 39 (APN 14) Group 2: 30 (APN 10). Age 4.9 y (range 2wk to12 yrs); 52F, uropathy 26 (VUR 10) Sample: SPA or 2 consecutive MSUs Exclusions: NS
Interventions	Group 1: Gentamicin IV 3 mg/kg single dose Group 2: 7 days of antibiotic according to sensitivity (TMP/SMX 16, amoxicillin 11, cephalosporins 3)
Outcomes	1. Persistent bacteriuria 1 day after therapy 2. Relapse within 1 week of end of therapy 3. Recurrent UTI 1 to 6 weeks after end of therapy
Notes	Definition of APN: UTI & fever > 38C, loin pain, systemic effects Duration: 6 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Hoberman 1999

Methods	Country: USA Multicentre tertiary centre IP & ED Randomisation: computer generated Power analysis: 128 per group to detect difference of 15% in renal scarring

Hoberman 1999 *(Continued)*

Participants	Age: 1 mo to 2 y Group 1: 153 (136F); age 8.8 (5.9SD) mo (range 1-24 mo). VUR 61 Group 2: 153 (137F); age 8.3 (5.6SD) mo (range 1-24 mo); VUR 54 Samples: catheter Exclusions: Clinically unstable patients, previous UTI, known uropathy, allergy to cephalosporins, other infections, gram positive cocci on stained urine
Interventions	Group 1: Cefixime 16 mg/kg on day 1 then 4 mg/kg/dose; 2 doses/d; 13 days Group 2: Cefotaxime 50 mg/kg/dose; 4 doses/d; 3 days or till afebrile then cefixime as group 1 to complete 14 days treatment
Outcomes	1. Scarring on DMSA at 6-7 months after UTI 2. Recurrent UTI in 6 months 3. Duration of fever
Notes	Definition of APN: UTI & fever > 38.3C Duration: 7 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Kafetzis 2000

Methods	Country: Greece Tertiary centre IP Randomisation method: NS but patients allocated on 2:1 basis Power analysis: NS
Participants	Age: 1 mo to 12 y Group 1: n = 10 Group 2: n = 6. Age 3 mo median (range 1-84 mths). Uropathy 4 Samples: SPA, catheter or 2 clean catch specimens Exclusions: Allergy to aminoglycosides, renal, hearing or vestibular dysfunction, antibiotics in previous 4 weeks, resistance to aminoglycosides
Interventions	Group 1: Isepamicin IV 7.5 mg/kg/dose; 2 doses/d; 10-14 days Group 2: Amikacin 7.5 mg/kg/dose; 2 doses/d; 10-14 days
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 & fever > 38C, systemic or local symptoms, CRP > 30mg/L, elevated ESR, WBC, pyuria Duration: 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement

Kafetzis 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Levtchenko 2001

Methods	Country: Belgium Tertiary centre IP/OPD Randomisation: NS Power analysis: NS
Participants	Age: 6 wk to 15 y Group 1: 43 (N of girls NS); age 25 mo median (range 2-182 mo); uropathy 5 Group 2: 44 (N of girls NS); age 20 mo median (range 3-179 mo); uropathy 1 Samples: SPA, MSU, 2-3 consecutive bag specimens Exclusions: negative urine culture, resistant organisms, severe uropathies, fever > 38oC within 24 h of randomisation
Interventions	Both groups given Temocillin IV 3days & then randomised Group 1: Temocillin IV (dose NS) for further 4 days then amoxicillin or amox/clav 50 mg/kg/dose; 3 doses/d; 14 days Group 2: Same oral antibiotics as group 1 given for 18 days
Outcomes	1. Persistent bacteriuria on day 7 of treatment 2. Recurrent UTI in 6wks after randomisation 3. Persistence of changes on DMSA at 6 months
Notes	Definition of APN: UTI & fever > 38.3C at start of IV therapy (afebrile at randomisation), systemic symptoms, loin pain, elevated WBC, ESR, CRP Duration: 6 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Montini 2003

Methods	Country: Italy Multicentre tertiary centres Randomisation: NS
Participants	Age: 2 mo to 6 y Group 1: n = 185; 1.09 (1.22SD) y Group 2: n = 202; 1.05 (1.25SD) y Females = 244 (63%) Urine collection: 2 consecutive urine cultures but method of collection not stated Exclusions: Abnormal renal function. Previous UTI
Interventions	Group 1: Oral amoxycillin/clavulinic acid 50 mg/kg/d for 10 days

Montini 2003 *(Continued)*

	Group 2: IV ceftriaxone 50 mg/kg/d till defervescence & oral amoxycillin/clavulinic acid 50 mg/kg/d to complete 10 day course
Outcomes	1. Time to defervescence 2. Renal parenchymal damage on DMSA scan at 1 year
Notes	Definition of APN: Fever, high inflammation indices (WBC, ESR, CRP) Duration of study: 1 year

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Pylkkänen 1981

Methods	Country: Finland Tertiary centre OPD Randomisation NS Not stratified for APN Power analysis: NS
Participants	Age: 0 to 13 y Group 1: 112 (73 APN); N of girls NS; age range 0 to12 y Group 2: 109 (76 APN); N of girls NS; age 0 to 12 y Sample: SPA or 2 consecutive MSU. Uropathy: 8 Exclusions: NS
Interventions	Group 1: Sulfafurazole oral 150-200 mg/kg/d in 3 doses; 10 days Group 2: Sulfafurazole as for Group 1; 42 days
Outcomes	1. Recurrent UTI during 12 months 2. Recurrent UTI by 1 month after ceasing therapy
Notes	Definition of APN: UTI & fever > 39C, ESR > 35, CRP > 20mg/L Duration: 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Repetto 1984

Methods	Country: Argentina Tertiary centre OPD Randomisation: NS Not stratified for APN Power analysis: NS

Repetto 1984 *(Continued)*

Participants	Age: 1 mo to14 y Group 1: 18 (17F); APN 4; median age 5 y; uropathy 2 Group 2: 19 (15F); APN 7; median age 6 y; uropathy 2 Sample: SPA, MSU Exclusions: allergy to cephalosporins, penicillins; renal failure; major uropathy
Interventions	Group 1: Cefotaxime IV 50 mg/kg single dose Group 2: Appropriate oral antibiotic for 10 days. TMP/SMX 14, nalidixic acid 2, nitrofurantoin 2, cephalexin 1, gentamicin 1
Outcomes	1. Persistent bacteriuria at 48 hours after end of treatment 2. Recurrent UTI at 30 days
Notes	Definition of APN: UTI & fever > 38C, loin pain Duration: 6 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Schaad 1998

Methods	Country: Europe Multicentre tertiary centres IP Randomisation: computer generated. Stratified by age Power analysis: 150 patients/group to ensure difference in eradication rates <12.6%
Participants	age: 1 mo to 12 y Group 1: 149 (83F); median age 1.7 y (range 0.1-12.9); uropathy 53 (VUR 33) Group 2: 150 (83F); age median 1.8 y (range 0.1-11.8); uropathy 56 (VUR 33) Samples: SPA, catheter, MSU, 2 consecutive bags Exclusions: Wt < 3kg, previous investigational drug, allergy to B-lactams, arginine; renal or liver dysfunction; immune deficiency
Interventions	Group 1: Cefepime IV 50 mg/kg/dose; 3 doses/d till afebrile for 48 hours. Then oral TMP/SMX for 10-14 days or further IV therapy Group 2: Ceftazidine IV 50 mg/kg/dose; 3 doses/d till afebrile for 48 hours. Then oral antibiotics as group 1
Outcomes	1. Persistent bacteriuria & unsatisfactory clinical response at end of IV therapy, end of antibiotic therapy 2. Recurrent UTI & unsatisfactory clinical response at 5-9 days & 4-6 weeks after end of therapy 3. Adverse effects
Notes	Definition of APN: UTI & fever > 38.5C & 1+ abdominal pain, loin pain, dysuria Duration: 6 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement

Schaad 1998 *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate

Toporovski 1992

Methods	Country: Brazil Tertiary centre IP/OPD Randomisation: computer generated Power analysis: NS
Participants	Age: 2-14 y Group 1: 26 (16F) Group 2: 11 (8F); VUR 6 Samples: MSU - 2 consecutive specimens Exclusions: Resistant organisms; renal or liver dysfunction; allergy to B-lactam antibiotics
Interventions	Group 1: Cefetamet pivoxil oral 10 mg/kg/dose (18) or 20 mg/kg/dose (8); 2 doses/d; 7-10 days Group 2: Amox/clav oral 30-50 mg/kg/dose; 3 doses/d; 7-10 days
Outcomes	1. Persistent bacteriuria or unsatisfactory clinical response at end of therapy & at 4-5 weeks 2. Adverse effects
Notes	Definition of APN: UTI & 2 + of fever > 37.5C, loin tenderness, dysuria, pyuria. Duration: 5 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Vigano 1992

Methods	Country: Italy Tertiary centre IP Randomisation: NS Power analysis: sample size chosen to detect 20% difference in effectiveness
Participants	Age: 1 mo to12 y Group 1: 74 (52F); mean age 2.01 y (range 0.08 to 10); uropathy 18 Group 2: 70 (50F); mean age 1.61 y (range 0.08 to 7); uropathy 23 Samples: clean catch or catheter. Exclusions: allergy to aminoglycosides; renal or hearing dysfunction; neuropathic bladder; urinary diversion
Interventions	Group 1: Netilmicin IM 5 mg/kg/d in 1 dose; 10 days Group 2: Netilmicin IM 2 mg/kg/dose; 3 doses/d; 10 days
Outcomes	1. Persistent bacteriuria at 7days & recurrent UTI by 30days after end of therapy 2. Adverse effects

Vigano 1992 *(Continued)*

Notes	Definition of APN: UTI & fever > 38.5C, ESR > 25, CRP > 20mg/L Duration: 6 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Vilaichone 2001

Methods	Country: Thailand Tertiary centre IP/OPD Randomisation: Blocks of four Power analysis: NS
Participants	Age: 1 mo to15 y Group 1: 18 (9F); mean age 26.7 (31.6SD) mo; VUR 3 Group 2: 18 (8F); mean age 14.8 (21.08SD) mo. VUR 4 Samples MSU, bag Exclusions: age < 1mo; previous UTI; known uropathy; allergic to trial antibiotics; renal failure; chronic disease; antibiotics in previous 48 hours
Interventions	Group 1: Ceftriaxone IV 75 mg/kg/d in single dose till fever resolved then oral ceftibuten 9 mg/kg/d (dose frequency NS). Total duration 10 days Group 2: Ceftriaxone IV 75 mg/kg/d in single dose; 10 days
Outcomes	1. Abnormal DMSA at 6 months 2. Recurrent UTI during 6 months 3. Persistent bacteriuria at end of treatment
Notes	Definition of APN: UTI & fever > 38C, subnormal temperature in infants, acute defects on DMSA Duration: 6 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

UTI = Urinary tract infection; VUR = Vesico-ureteric reflux; ED = Emergency Department; IP = Inpatient; OPD = Outpatient department; MSU = Mid stream urine specimen; APN = Acute pyelonephritis; TMP/SMX = Trimethoprim/sulphamethoxazole; Amox/clav = Amoxycillin/clavulanic acid; NS = not stated; DMSA = Tc99m - dimercaptosuccinic acid nuclear scan; SPA = suprapubic bladder aspiration; CRP = C reactive protein; WBC = White blood count; ESR = Erythrocyte sedimentation rate

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

Study	Reason for exclusion
Bose 1974	Quasi randomised controlled trial. Cannot separate data on children with pyelonephritis from those with lower urinary tract infection.

Study	Reason for exclusion
Clemente 1994	Randomised controlled trial of immunomodulating agents not antibiotics in acute pyelonephritis.
Dagan 1992	Randomised controlled trial. Cannot separate data on children with acute pyelonephritis from those with lower urinary tract infection.
Ellerstein 1977	Randomised controlled trial. Unclear as to whether patients with pyelonephritis included.
Francois 1995	Randomised controlled trial comparing 7 days of cefixime with amoxicillin/clavulinic acid. Cannot separate data on children with acute pyelonephritis from those with lower urinary tract infection.
Gok 2001	Randomised controlled trial. Cannot separate data on children with acute pyelonphritis from those with lower urinary tract infection.
Howard 1978	Randomised controlled trial. Cannot separate data on children with acute pyelonephritis from those with lower urinary tract infection.
Khan 1981	Randomised controlled trial comparing 3 days to 10 days of antibiotics. Episodes of UTI reported rather than patients. Reported on 11 episodes of acute pyelonephritis among 62 episodes of UTI.
Lake 1971	Randomised controlled trial. Urinary tract infection but cannot separate data for febrile children from adult data.
Pitt 1982	Randomised controlled trial. Cannot separate data on children with acute pyelonephritis from those with lower urinary tract infection.
Russo 1977	Randomised controlled trial. Cannot separate data on children with acute pyelonephritis from those with lower urinary tract infection.

DATA AND ANALYSES

Comparison 1. Oral (14 days) versus intravenous (3 days) 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 (hours)	2	693	Mean Difference (IV, Random, 95% CI)	1.54 [-1.67, 4.76]
2 Recurrent UTI within 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Total urinary tract infections	1	287	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.28, 1.51]
2.2 Symptomatic urinary tract infections	1	287	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.27, 1.67]

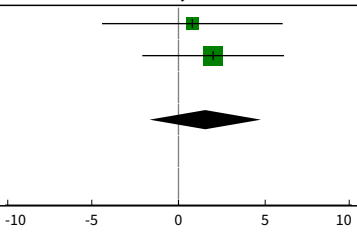
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Renal parenchymal damage at 6 months	1	272	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.69, 3.03]
4 Proportion of renal parenchyma with damage at 6 months	1	272	Mean Difference (IV, Random, 95% CI)	-0.70 [-1.74, 0.34]
5 Renal damage at 6 months: post hoc subgroup analysis	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Persistent damage in children with DMSA changes at UTI	1	187	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.62, 2.43]
5.2 Persistent damage in children without VUR	1	165	Risk Ratio (M-H, Random, 95% CI)	0.8 [0.23, 2.73]
5.3 Persistent damage in children with VUR	1	107	Risk Ratio (M-H, Random, 95% CI)	1.88 [0.83, 4.24]
5.4 Persistent renal damage with VUR grades 1-2	1	61	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.16, 2.61]
5.5 Persistent damage with VUR grades 3-5	1	46	Risk Ratio (M-H, Random, 95% CI)	7.33 [1.00, 54.01]

Analysis 1.1. Comparison 1 Oral (14 days) versus intravenous (3 days) followed by oral (11 days) therapy, Outcome 1 Time to fever resolution (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	Weight	Mean Difference Random, 95% CI
Hoberman 1999	153	24.7 (23.2)	153	23.9 (23.3)		38.09%	0.8[-4.41,6.01]
Montini 2003	185	36.9 (20.2)	202	34.9 (20.8)		61.91%	2[-2.09,6.09]
Total * **	**338**		**355**			**100%**	**1.54[-1.67,4.76]**

Heterogeneity: $Tau^2=0$; $Chi^2=0.13$, df=1(P=0.72); $I^2=0\%$

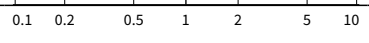
Test for overall effect: Z=0.94(P=0.35)

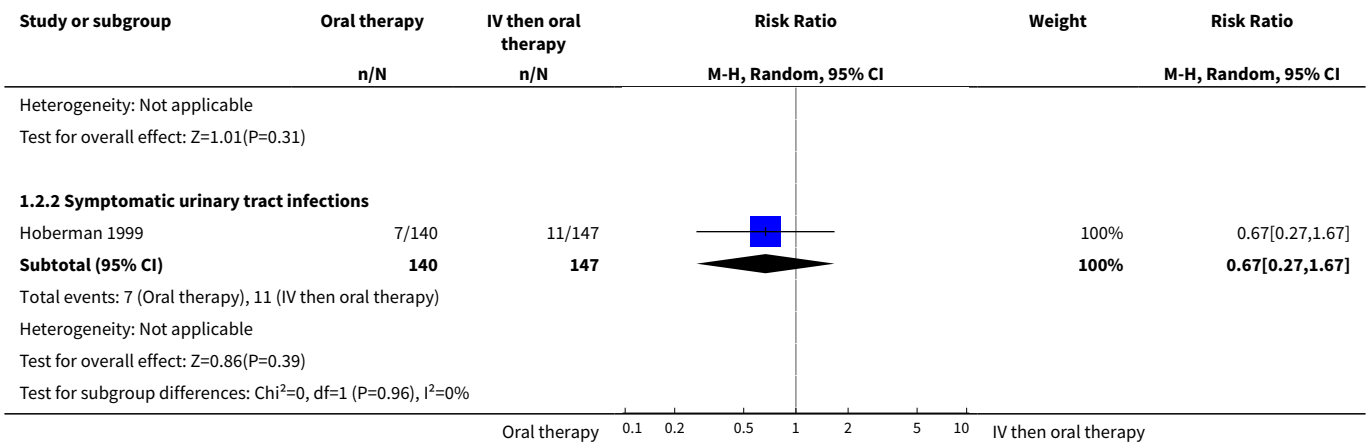


Analysis 1.2. Comparison 1 Oral (14 days) versus intravenous (3 days) followed by oral (11 days) therapy, Outcome 2 Recurrent UTI within 6 months.

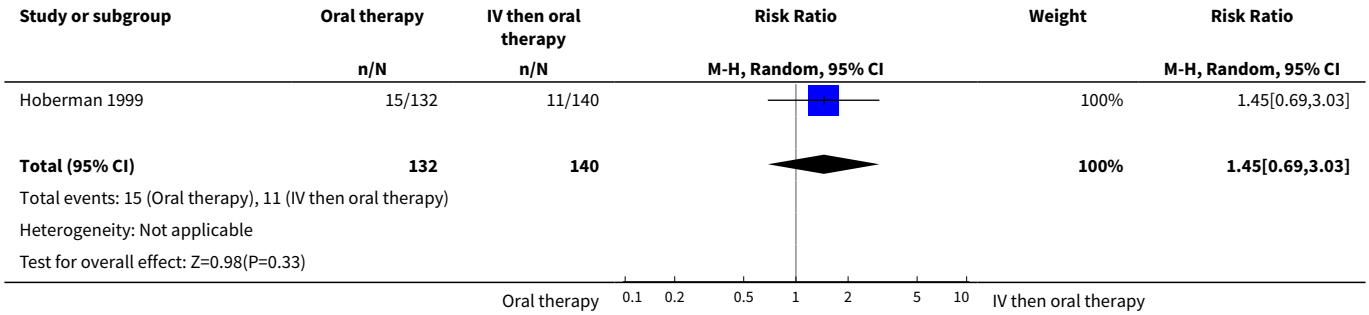
Study or subgroup	Oral therapy n/N	IV then oral therapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Total urinary tract infections					
Hoberman 1999	8/140	13/147		100%	0.65[0.28,1.51]
Subtotal (95% CI)	**140**	**147**		**100%**	**0.65[0.28,1.51]**

Total events: 8 (Oral therapy), 13 (IV then oral therapy)

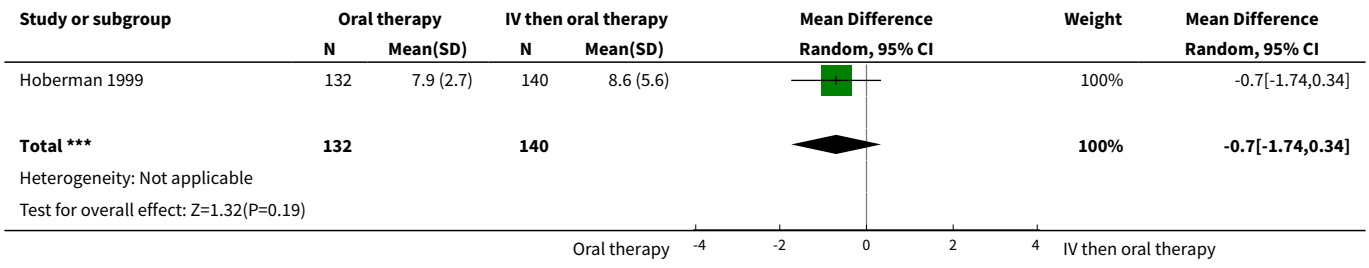




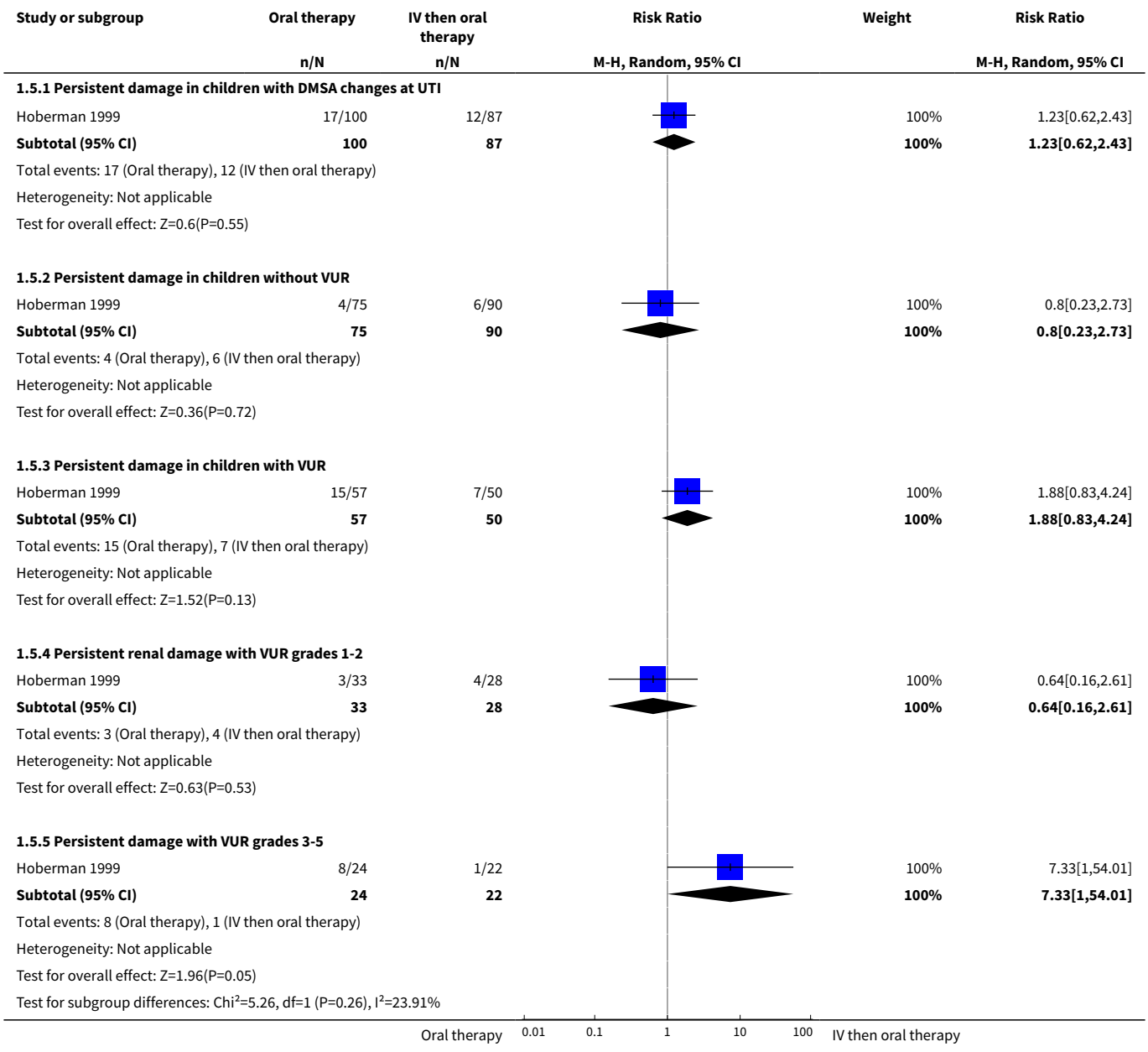
Analysis 1.3. Comparison 1 Oral (14 days) versus intravenous (3 days) followed by oral (11 days) therapy, Outcome 3 Renal parenchymal damage at 6 months.



Analysis 1.4. Comparison 1 Oral (14 days) versus intravenous (3 days) followed by oral (11 days) therapy, Outcome 4 Proportion of renal parenchyma with damage at 6 months.



Analysis 1.5. Comparison 1 Oral (14 days) versus intravenous (3 days) followed by oral (11 days) therapy, Outcome 5 Renal damage at 6 months: post hoc subgroup analysis.



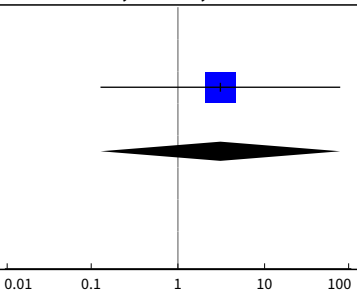
Comparison 2. Short duration (3-4 days) versus long duration (7-14 days) intravenous therapy

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Persistent bacteriuria after treatment	3	251	Risk Ratio (M-H, Random, 95% CI)	3.09 [0.13, 74.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Recurrent UTI within 6 months	4	445	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.52, 2.51]
3 Persistent renal damage at 3-6 months	3	315	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.72, 1.37]
4 Persistent renal 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]
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 < 7days 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) intravenous therapy, Outcome 1 Persistent bacteriuria after treatment.

Study or subgroup	Oral then IV therapy n/N	IV therapy only 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		100%	3.09[0.13,74.55]
Total (95% CI)	**125**	**126**		**100%**	**3.09[0.13,74.55]**
Total events: 1 (Oral then IV therapy), 0 (IV therapy only)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.7(P=0.49)					



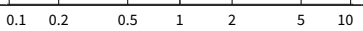
Analysis 2.2. Comparison 2 Short duration (3-4 days) versus long duration (7-14 days) intravenous therapy, Outcome 2 Recurrent UTI within 6 months.

Study or subgroup	Oral then IV therapy n/N	IV therapy only n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Benador 2001	9/110	6/110		61.48%	1.5[0.55,4.07]
Francois 1997	0/49	2/53		6.76%	0.22[0.01,4.39]
Levtchenko 2001	2/44	3/43		20.27%	0.65[0.11,3.71]
Vilaichone 2001	2/18	1/18		11.49%	2[0.2,20.15]
Total (95% CI)	**221**	**224**		**100%**	**1.15[0.52,2.51]**
Total events: 13 (Oral then IV therapy), 12 (IV therapy only)					
Heterogeneity: Tau^2=0; Chi^2=2.11, df=3(P=0.55); I^2=0%					
Test for overall effect: Z=0.35(P=0.73)					

Oral then IV therapy — IV therapy only

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

Study or subgroup	Oral then IV therapy n/N	IV therapy only n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Benador 2001	40/110	36/110		50.68%	1.11[0.77,1.6]
Levtchenko 2001	8/33	11/26		16.3%	0.57[0.27,1.22]
Vilaichone 2001	12/18	11/18		33.02%	1.09[0.67,1.79]
Total (95% CI)	**161**	**154**		**100%**	**0.99[0.72,1.37]**
Total events: 60 (Oral then IV therapy), 58 (IV therapy only)					
Heterogeneity: Tau^2=0.02; Chi^2=2.55, df=2(P=0.28); I^2=21.71%					
Test for overall effect: Z=0.05(P=0.96)					

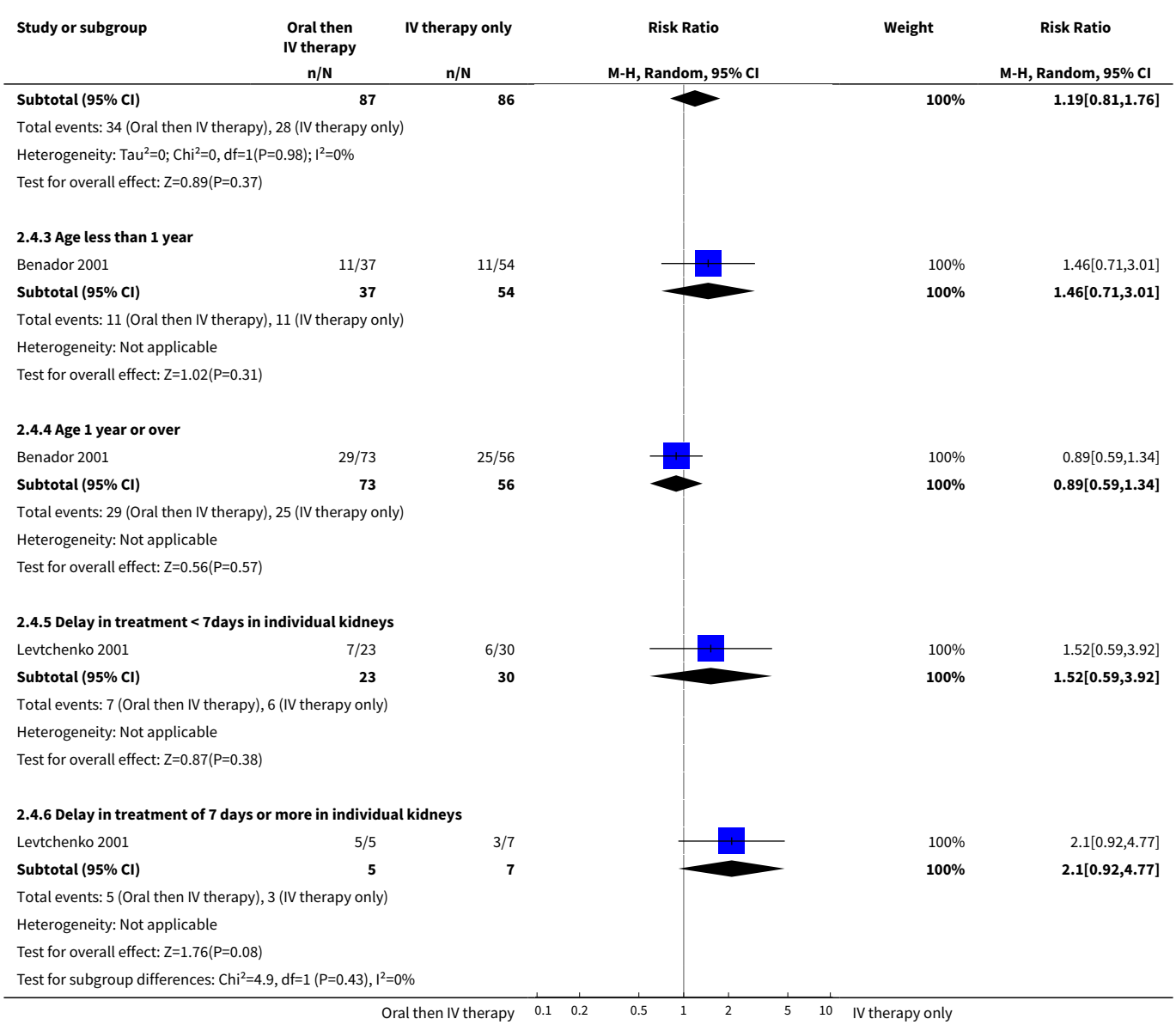


Oral then IV therapy — IV therapy only

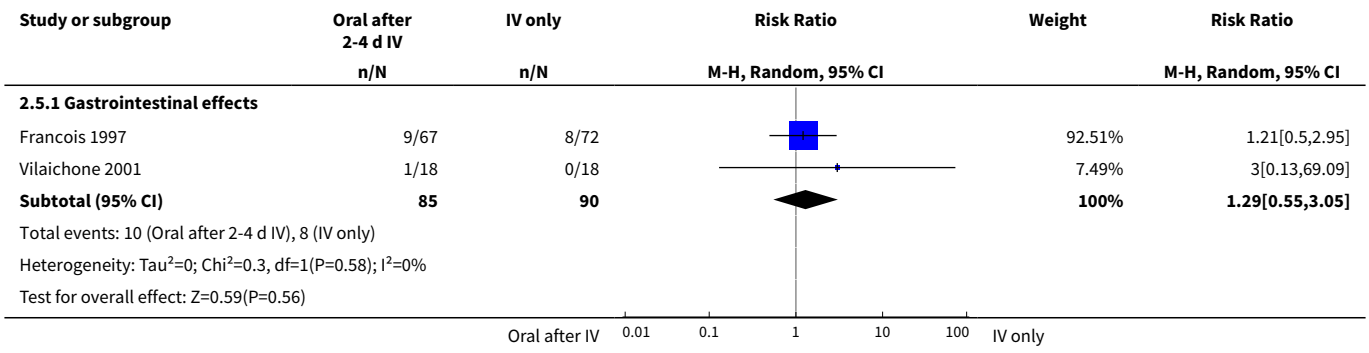
Analysis 2.4. Comparison 2 Short duration (3-4 days) versus long duration (7-14 days) intravenous therapy, Outcome 4 Persistent renal damage at 3-6 months - post hoc subgroup analysis.

Study or subgroup	Oral then IV therapy n/N	IV therapy only 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 (Oral then IV therapy), 19 (IV therapy only)					
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]

Oral then IV therapy — IV therapy only



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

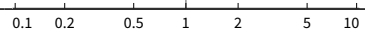


Comparison 3. Single dose parenteral therapy and oral therapy versus oral therapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent bacteriuria at 48 hours	1	69	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.19, 3.20]
2 Treatment failure after 48 hours of therapy	1	69	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.24, 2.81]
3 Recurrent UTI within 1 month	1	69	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Total adverse events	1	69	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.33, 5.68]
4.2 Gastrointestinal adverse events	1	69	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.22, 4.75]

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

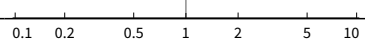
Study or subgroup	Ceftriaxone/TMP+SMX n/N	TMP+SMX n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Baker 2001	3/34	4/35		100%	0.77[0.19,3.2]
Total (95% CI)	**34**	**35**		**100%**	**0.77[0.19,3.2]**
Total events: 3 (Ceftriaxone/TMP+SMX), 4 (TMP+SMX)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.36(P=0.72)					



Ceftriaxone/TMP+SMX TMP+SMX

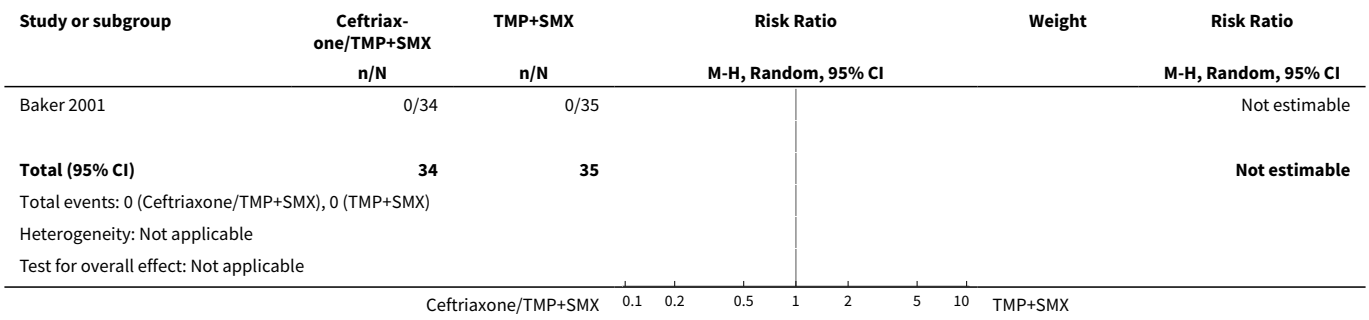
Analysis 3.2. Comparison 3 Single dose parenteral therapy and oral therapy versus oral therapy alone, Outcome 2 Treatment failure after 48 hours of therapy.

Study or subgroup	Ceftriaxone/TMP+SMX n/N	TMP+SMX n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Baker 2001	4/34	5/35		100%	0.82[0.24,2.81]
Total (95% CI)	**34**	**35**		**100%**	**0.82[0.24,2.81]**
Total events: 4 (Ceftriaxone/TMP+SMX), 5 (TMP+SMX)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.31(P=0.76)					

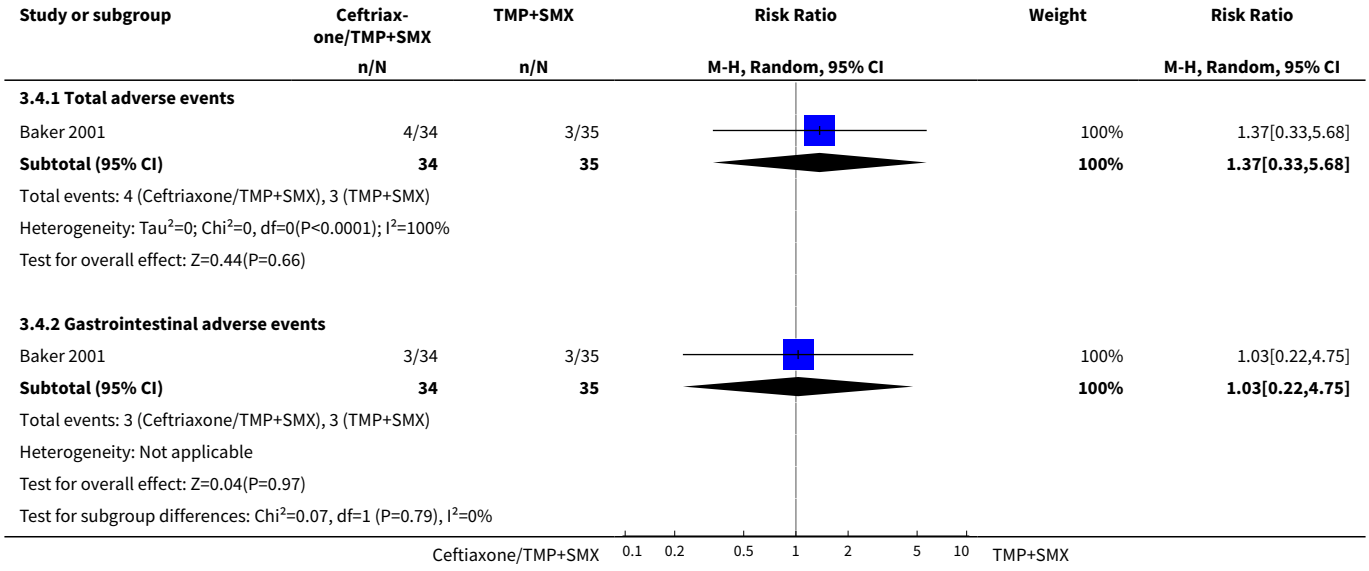


Ceftriaxone/TMP+SMX TMP+SMX

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



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



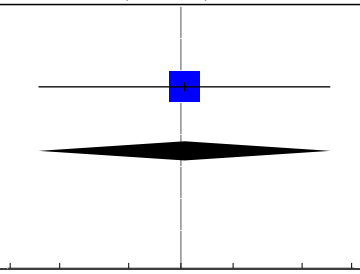
Comparison 4. Different dosing regimens of aminoglycosides (daily versus 8 hourly)

Outcome or subgroup title	No. of studies	No. of partici-pants	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	179	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.37, 10.53]
3 Persistent bacteriuria at 1 week after treatment	1	144	Risk Ratio (M-H, Random, 95% CI)	2.84 [0.12, 68.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Reinfection at 1 month after completing treatment	1	144	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.33, 4.23]
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 defervescence	1	172	Mean Difference (IV, Random, 95% CI)	2.40 [-7.90, 12.70]
8 Renal parenchymal damage at 3 months	1	146	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.32, 1.36]

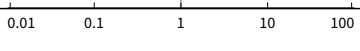
Analysis 4.1. Comparison 4 Different dosing regimens of aminoglycosides (daily versus 8 hourly), Outcome 1 Persistent bacteriuria after 1-3 days of treatment.

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
Carapetis 2001	0/60	0/59			Not estimable
Vigano 1992	0/74	0/70			Not estimable
Chong 2003	2/84	2/88		100%	1.05[0.15,7.27]
Total (95% CI)	**218**	**217**		**100%**	**1.05[0.15,7.27]**
Total events: 2 (Daily treatment), 2 (8 hourly treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.05(P=0.96)					



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.

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	4/90	2/89		100%	1.98[0.37,10.53]
Total (95% CI)	**90**	**89**		**100%**	**1.98[0.37,10.53]**
Total events: 4 (Daily treatment), 2 (8 hourly treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.8(P=0.42)					



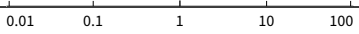
Analysis 4.3. Comparison 4 Different dosing regimens of aminoglycosides (daily versus 8 hourly), Outcome 3 Persistent bacteriuria at 1 week after treatment.

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	1/74	0/70		100%	2.84[0.12,68.57]
Total (95% CI)	**74**	**70**		**100%**	**2.84[0.12,68.57]**
Total events: 1 (Daily treatment), 0 (8 hourly treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					

Daily treatment 8 hourly treatment

Analysis 4.4. Comparison 4 Different dosing regimens of aminoglycosides (daily versus 8 hourly), Outcome 4 Reinfection at 1 month after completing 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	5/74	4/70		100%	1.18[0.33,4.23]
Total (95% CI)	**74**	**70**		**100%**	**1.18[0.33,4.23]**
Total events: 5 (Daily treatment), 4 (8 hourly treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.26(P=0.8)					



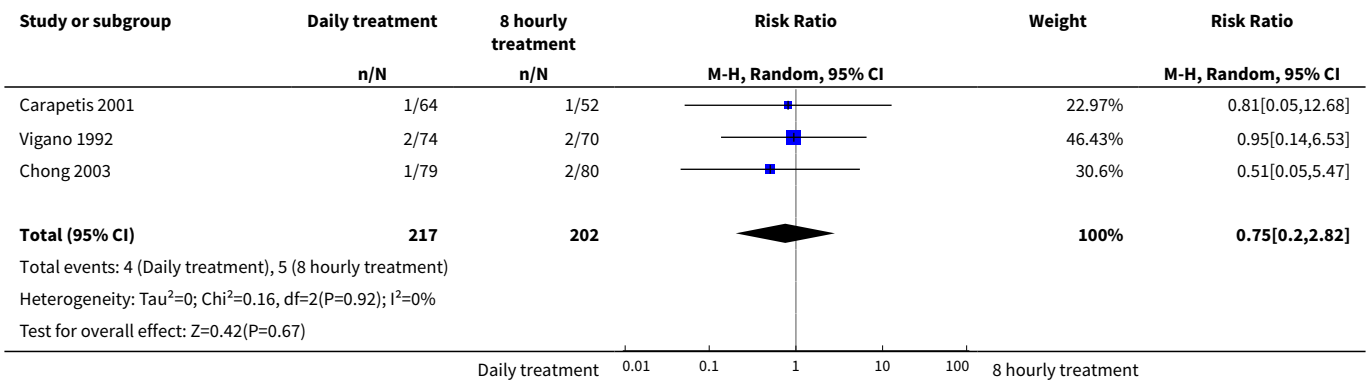
Daily treatment 8 hourly treatment

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

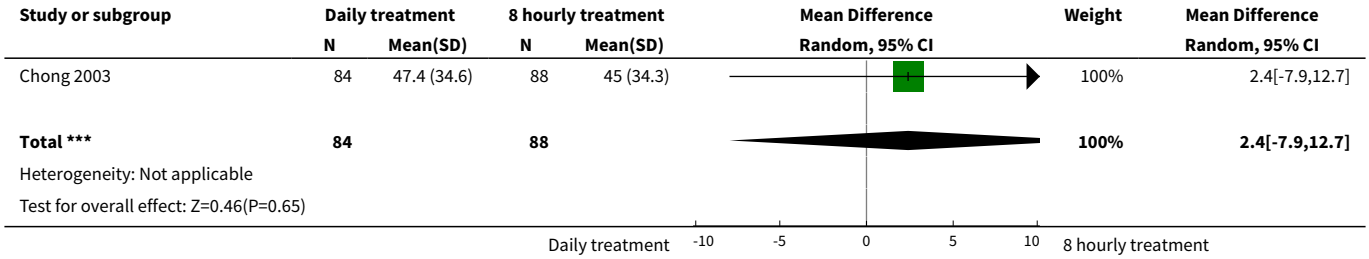
Study or subgroup	Daily treatment n/N	8 hourly treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Carapetis 2001	1/39	0/33		46.55%	2.55[0.11,60.57]
Vigano 1992	2/20	0/12		53.45%	3.1[0.16,59.52]
Chong 2003	0/79	0/88			Not estimable
Total (95% CI)	**138**	**133**		**100%**	**2.83[0.33,24.56]**
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)					

Daily treatment 8 hourly treatment

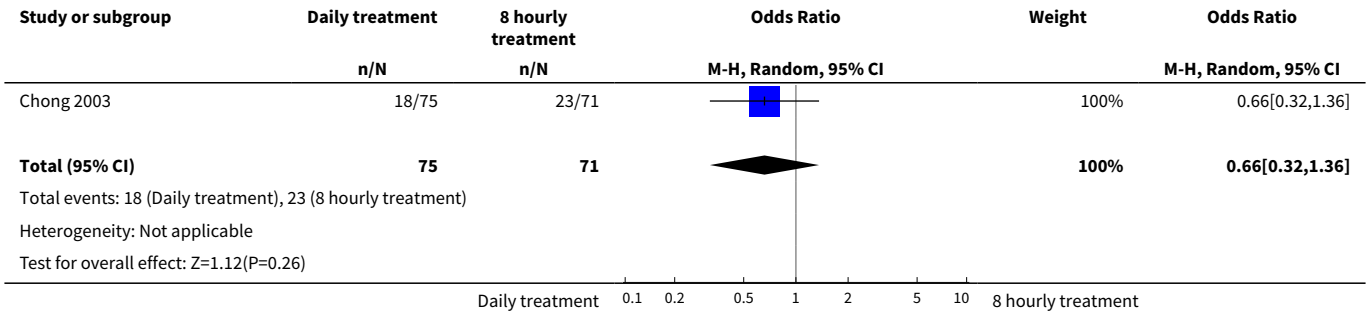
Analysis 4.6. Comparison 4 Different dosing regimens of aminoglycosides (daily versus 8 hourly), Outcome 6 Increase in serum creatinine during treatment.



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



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

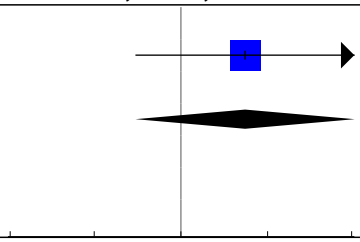


Comparison 5. Agent: 3rd generation cephalosporin versus amoxycillin + clavulanic acid

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Persistent bacteriuria after 48 hours of therapy	2	56	Risk Ratio (M-H, Random, 95% CI)	5.50 [0.30, 101.28]
2 Recurrent UTI at 7-10 days after end of therapy	2	57	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Persistent symptoms at 7-10 days after end of treatment	1	37	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Number with fever for > 48 hours	1	20	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.27, 92.62]
5 Gastrointestinal adverse events	2	57	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.03, 13.52]

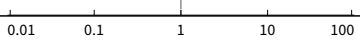
Analysis 5.1. Comparison 5 Agent: 3rd generation cephalosporin versus amoxycillin + clavulanic acid, Outcome 1 Persistent bacteriuria after 48 hours of therapy.

Study or subgroup	Cephalosporin n/N	Amox-il/clavulinate 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		100%	5.5[0.3,101.28]
Total (95% CI)	**35**	**21**		**100%**	**5.5[0.3,101.28]**
Total events: 2 (Cephalosporin), 0 (Amoxil/clavulinate)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.15(P=0.25)					

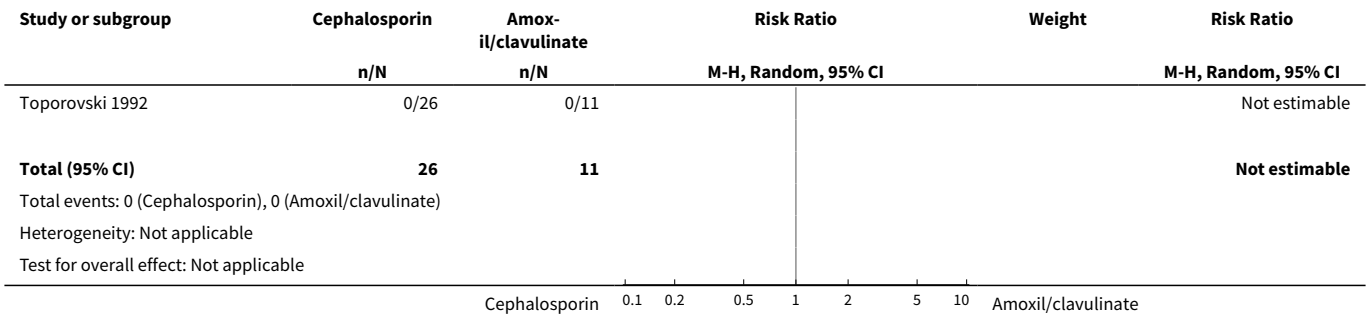


Analysis 5.2. Comparison 5 Agent: 3rd generation cephalosporin versus amoxycillin + clavulanic acid, Outcome 2 Recurrent UTI at 7-10 days after end of therapy.

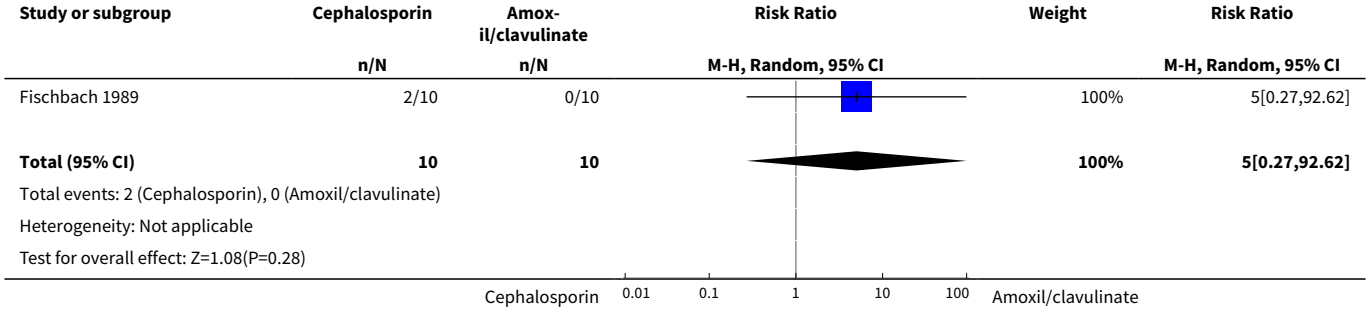
Study or subgroup	Cephalosporin n/N	Amox-il/clavulinate n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Toporovski 1992	0/26	0/11			Not estimable
Fischbach 1989	0/10	0/10			Not estimable
Total (95% CI)	**36**	**21**			**Not estimable**
Total events: 0 (Cephalosporin), 0 (Amoxil/clavulinate)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



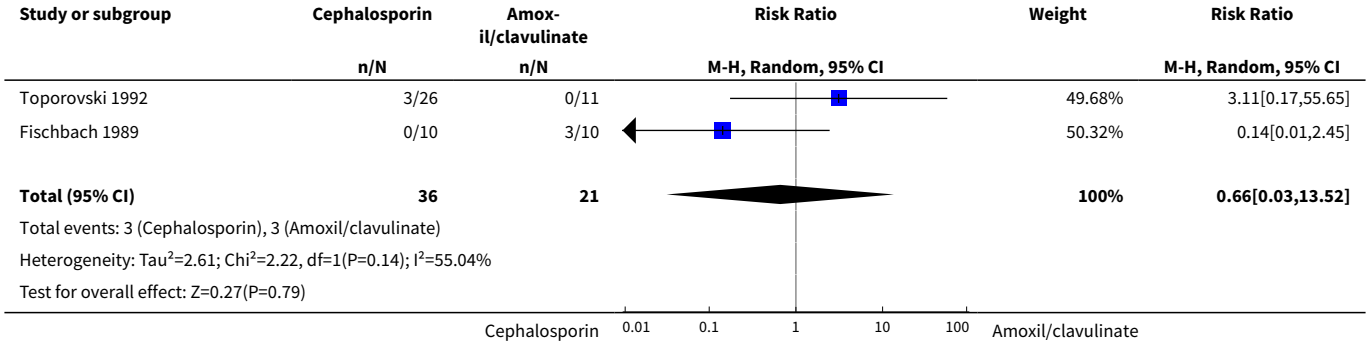
Analysis 5.3. Comparison 5 Agent: 3rd generation cephalosporin versus amoxycillin + clavulanic acid, Outcome 3 Persistent symptoms at 7-10 days after end of treatment.



Analysis 5.4. Comparison 5 Agent: 3rd generation cephalosporin versus amoxycillin + clavulanic acid, Outcome 4 Number with fever for > 48 hours.



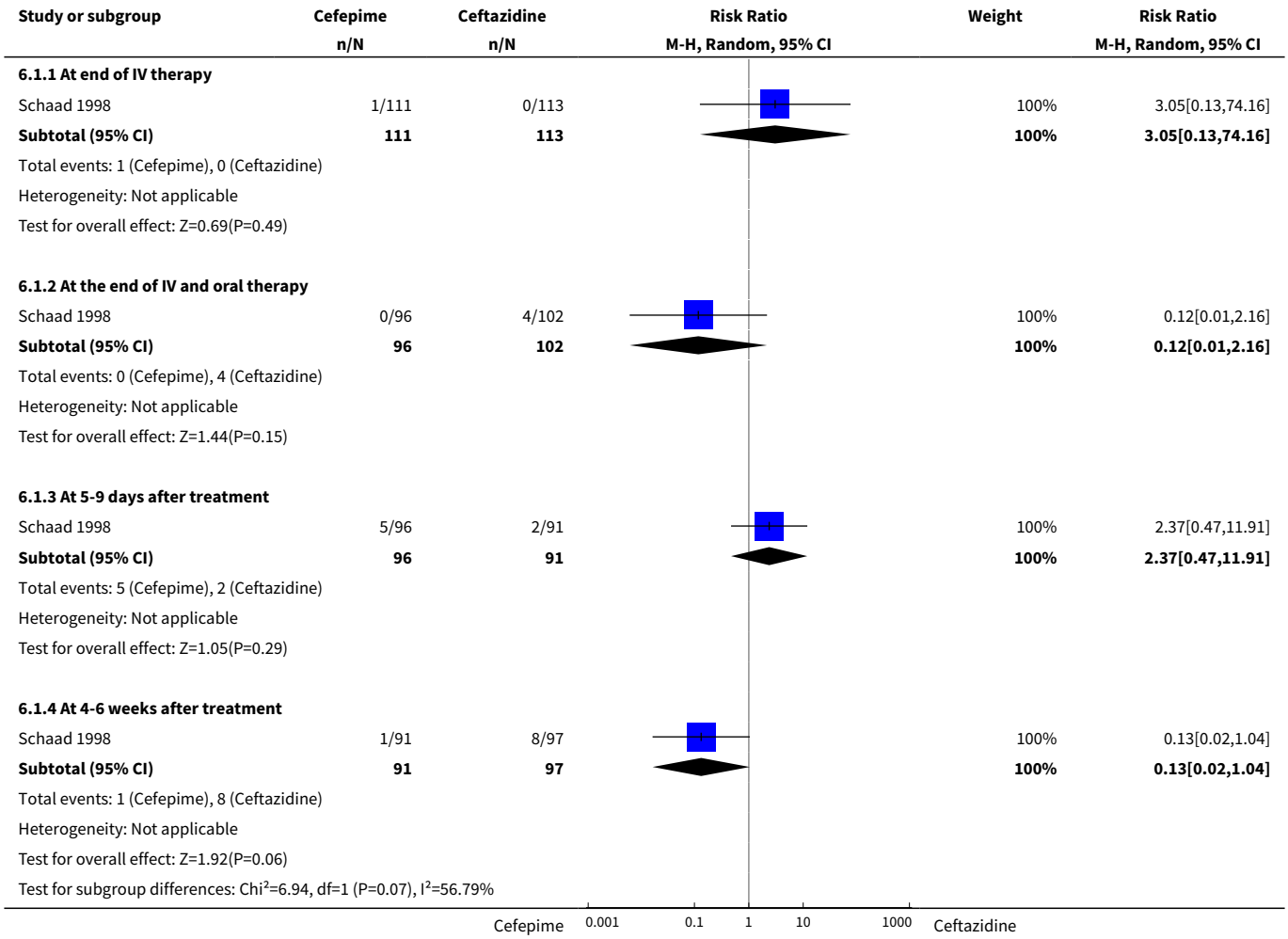
Analysis 5.5. Comparison 5 Agent: 3rd generation cephalosporin versus amoxycillin + clavulanic acid, Outcome 5 Gastrointestinal adverse events.



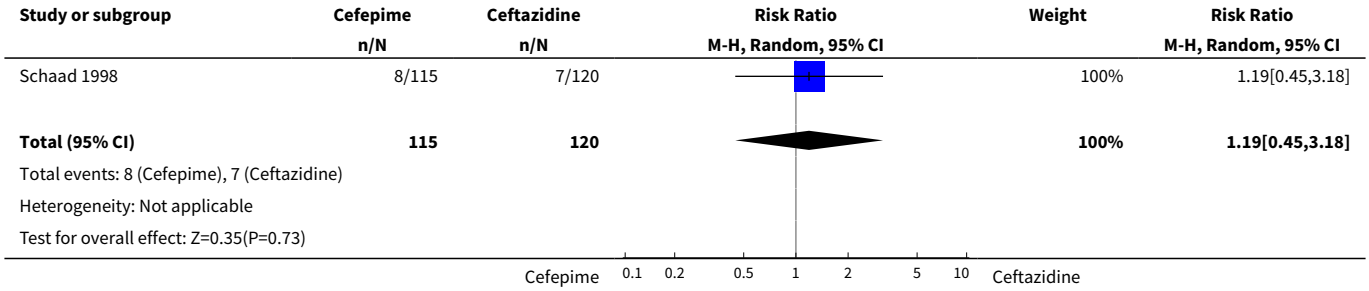
Comparison 6. Agent: Cefipime versus Ceftazidime

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)	Subtotals only
1.1 At end of IV therapy	1	224	Risk Ratio (M-H, Random, 95% CI)	3.05 [0.13, 74.16]
1.2 At the end of IV and oral therapy	1	198	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.01, 2.16]
1.3 At 5-9 days after treatment	1	187	Risk Ratio (M-H, Random, 95% CI)	2.37 [0.47, 11.91]
1.4 At 4-6 weeks after treatment	1	188	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.02, 1.04]
2 Infection with new pathogen at 4-6 weeks	1	235	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.45, 3.18]
3 Unsatisfactory clinical response	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 At end of IV therapy	1	233	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.12, 4.02]
3.2 At end of IV and oral therapy	1	202	Risk Ratio (M-H, Random, 95% CI)	5.10 [0.25, 104.90]
3.3 At 5-9 days after treatment	1	199	Risk Ratio (M-H, Random, 95% CI)	5.05 [0.25, 103.87]
3.4 At 4-6 weeks after treatment	1	200	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.06, 1.27]
4 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Total adverse events	1	299	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.76, 1.63]
4.2 Drug-related adverse effects	1	299	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.65, 3.07]
4.3 Gastrointestinal adverse effects	1	299	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.47, 2.67]
4.4 Cutaneous adverse effects	1	299	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.26, 8.91]
4.5 Discontinuation due to drug related adverse effects	1	299	Risk Ratio (M-H, Random, 95% CI)	4.03 [0.46, 35.61]

Analysis 6.1. Comparison 6 Agent: Cefipime versus Ceftazidime, Outcome 1 Persistence or recurrence of initial pathogen.

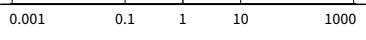


Analysis 6.2. Comparison 6 Agent: Cefipime versus Ceftazidime, Outcome 2 Infection with new pathogen at 4-6 weeks.



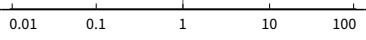
Analysis 6.3. Comparison 6 Agent: Cefipime versus Ceftazidime, Outcome 3 Unsatisfactory clinical response.

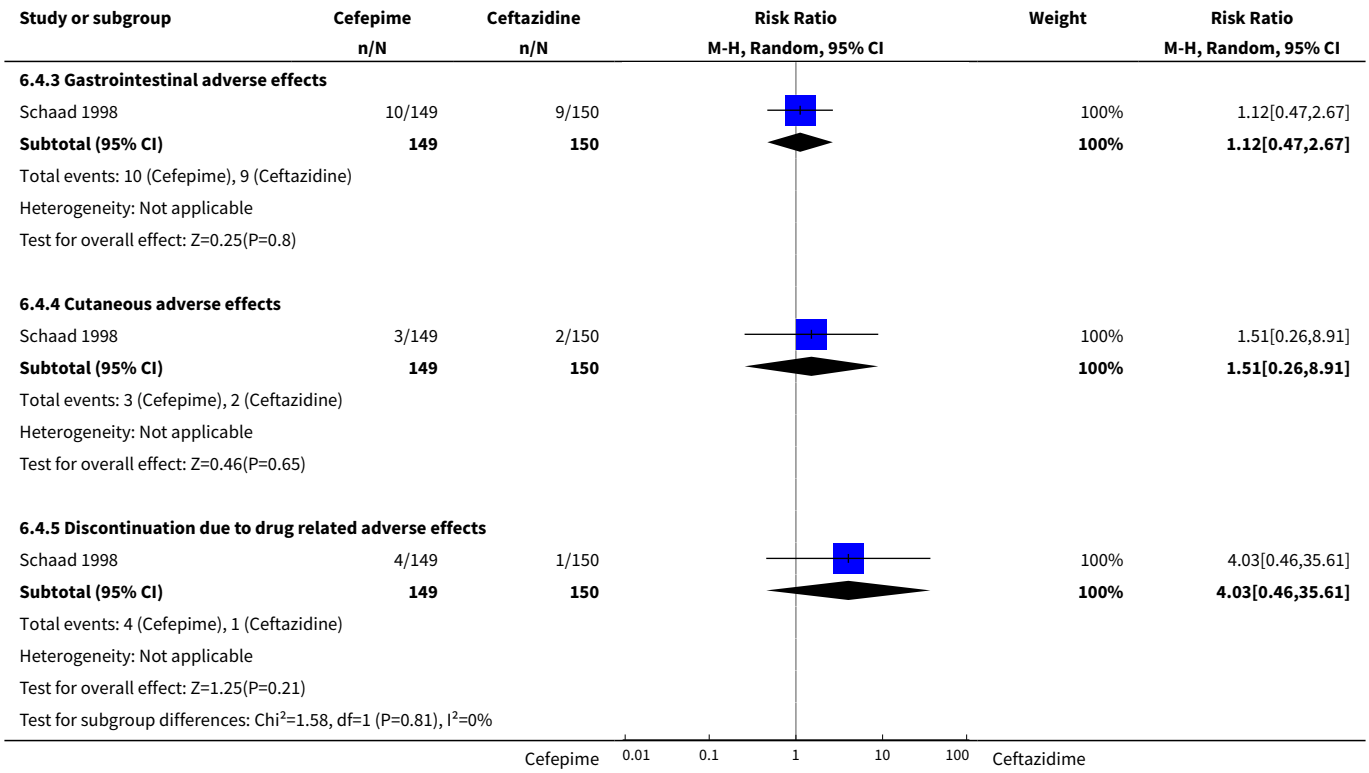
Study or subgroup	Cefepime n/N	Ceftazidine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 At end of IV therapy					
Schaad 1998	2/115	3/118		100%	0.68[0.12,4.02]
Subtotal (95% CI)	**115**	**118**		**100%**	**0.68[0.12,4.02]**
Total events: 2 (Cefepime), 3 (Ceftazidine)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.42(P=0.67)					
6.3.2 At end of IV and oral therapy					
Schaad 1998	2/100	0/102		100%	5.1[0.25,104.9]
Subtotal (95% CI)	**100**	**102**		**100%**	**5.1[0.25,104.9]**
Total events: 2 (Cefepime), 0 (Ceftazidine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.06(P=0.29)					
6.3.3 At 5-9 days after treatment					
Schaad 1998	2/99	0/100		100%	5.05[0.25,103.87]
Subtotal (95% CI)	**99**	**100**		**100%**	**5.05[0.25,103.87]**
Total events: 2 (Cefepime), 0 (Ceftazidine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.29)					
6.3.4 At 4-6 weeks after treatment					
Schaad 1998	2/95	8/105		100%	0.28[0.06,1.27]
Subtotal (95% CI)	**95**	**105**		**100%**	**0.28[0.06,1.27]**
Total events: 2 (Cefepime), 8 (Ceftazidine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.65(P=0.1)					
Test for subgroup differences: Chi^2=4.72, df=1 (P=0.19), I^2=36.49%					



Analysis 6.4. Comparison 6 Agent: Cefipime versus Ceftazidime, Outcome 4 Adverse effects.

Study or subgroup	Cefepime n/N	Ceftazidine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.4.1 Total adverse events					
Schaad 1998	41/149	37/150		100%	1.12[0.76,1.63]
Subtotal (95% CI)	**149**	**150**		**100%**	**1.12[0.76,1.63]**
Total events: 41 (Cefepime), 37 (Ceftazidine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.56(P=0.58)					
6.4.2 Drug-related adverse effects					
Schaad 1998	14/149	10/150		100%	1.41[0.65,3.07]
Subtotal (95% CI)	**149**	**150**		**100%**	**1.41[0.65,3.07]**
Total events: 14 (Cefepime), 10 (Ceftazidine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.86(P=0.39)					





Comparison 7. Agent: Ceftriaxone versus Cefotaxime

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent bacteriuria at 48 hours	1	100	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Bacteriuria 10 days after end of treatment	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 All patients	1	83	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.37, 2.03]
2.2 Normal renal tract imaging	1	55	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.42, 4.65]
2.3 Abnormal renal tract imaging	1	45	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.14, 1.94]
3 UTI at 1 month after therapy	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 All patients	1	81	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.30, 1.50]
3.2 Normal renal tract imaging	1	55	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.27, 2.97]

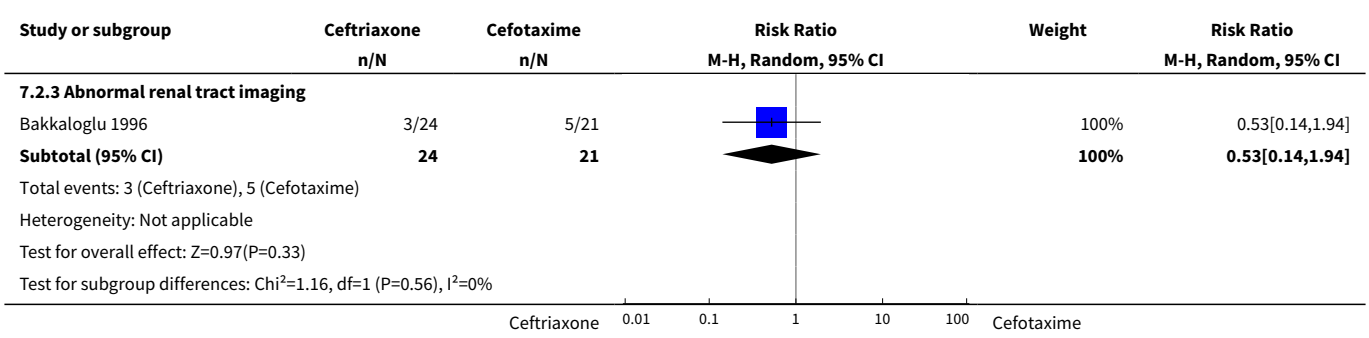
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.3 Abnormal renal tract imaging	1	45	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.19, 1.79]
4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 All adverse events	1	100	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.12, 3.82]
4.2 Skin eruptions	1	100	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.10]
4.3 Gastrointestinal adverse events	1	100	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 71.92]

Analysis 7.1. Comparison 7 Agent: Ceftriaxone versus Cefotaxime, Outcome 1 Persistent bacteriuria at 48 hours.

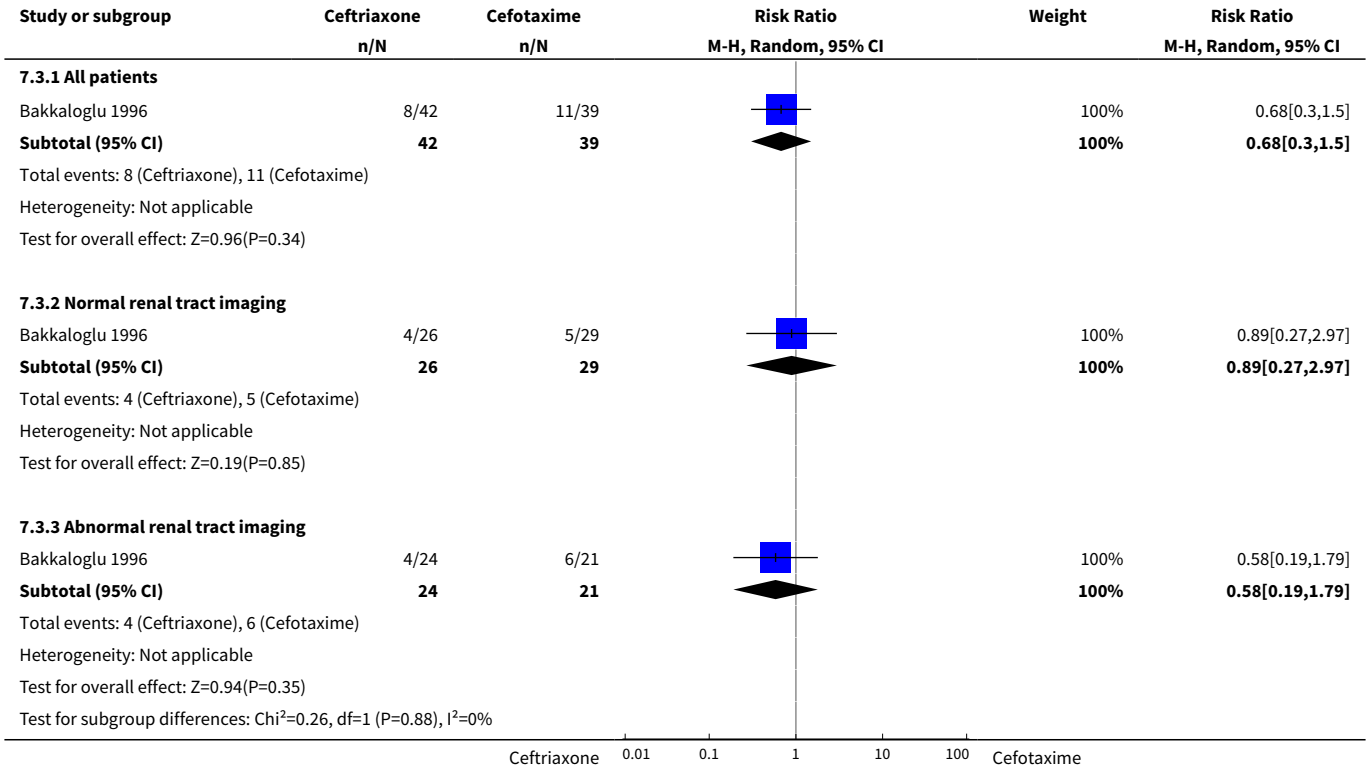
Study or subgroup	Ceftriaxone n/N	Cefotaxime n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bakkaloglu 1996	0/50	0/50			Not estimable
Total (95% CI)	**50**	**50**			**Not estimable**
Total events: 0 (Ceftriaxone), 0 (Cefotaxime)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

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

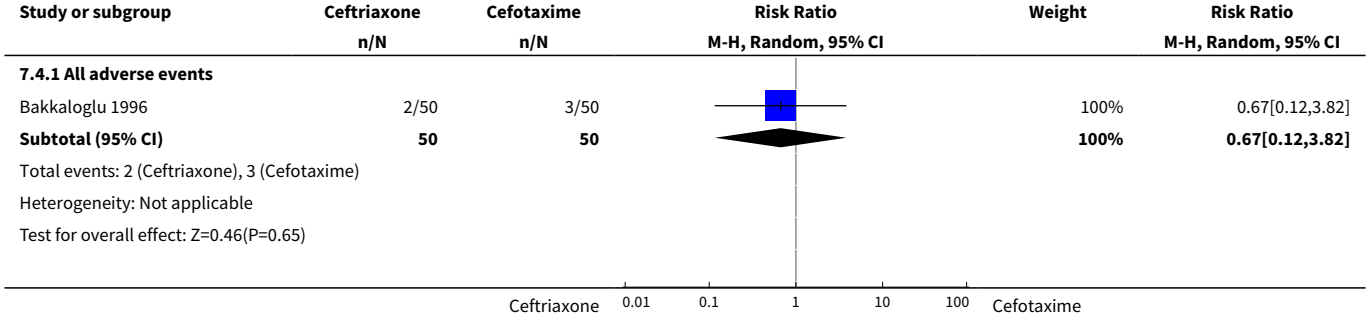
Study or subgroup	Ceftriaxone n/N	Cefotaxime n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.2.1 All patients					
Bakkaloglu 1996	8/42	9/41		100%	0.87[0.37,2.03]
Subtotal (95% CI)	**42**	**41**		**100%**	**0.87[0.37,2.03]**
Total events: 8 (Ceftriaxone), 9 (Cefotaxime)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.33(P=0.74)					
7.2.2 Normal renal tract imaging					
Bakkaloglu 1996	5/26	4/29		100%	1.39[0.42,4.65]
Subtotal (95% CI)	**26**	**29**		**100%**	**1.39[0.42,4.65]**
Total events: 5 (Ceftriaxone), 4 (Cefotaxime)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					

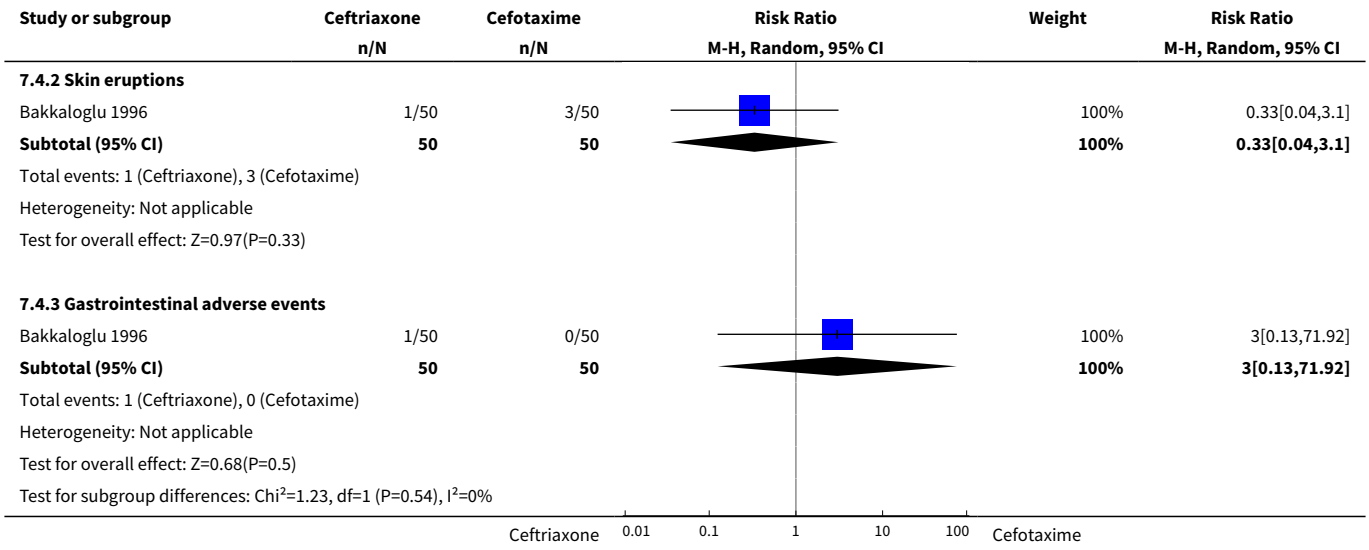


Analysis 7.3. Comparison 7 Agent: Ceftriaxone versus Cefotaxime, Outcome 3 UTI at 1 month after therapy.



Analysis 7.4. Comparison 7 Agent: Ceftriaxone versus Cefotaxime, Outcome 4 Adverse events.

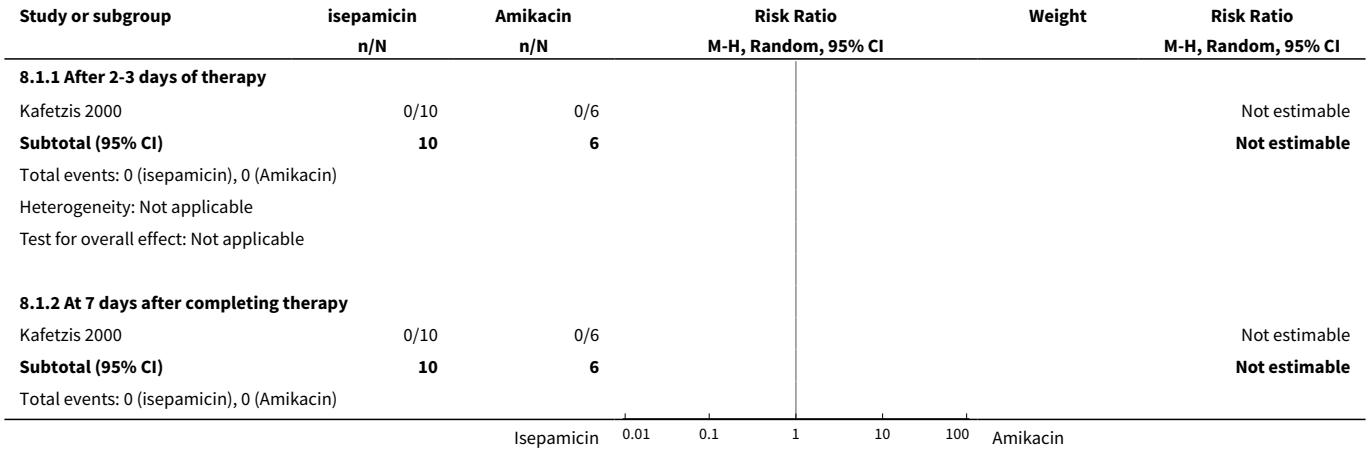


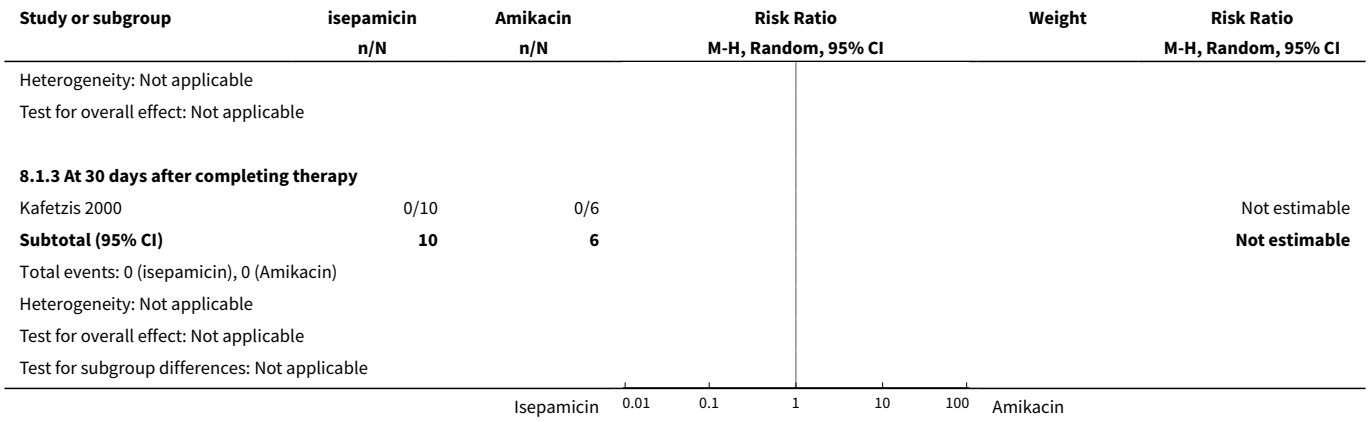


Comparison 8. Agent: Isepamicin versus Amikacin

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)	Subtotals only
1.1 After 2-3 days of therapy	1	16	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 At 7 days after completing therapy	1	16	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 At 30 days after completing therapy	1	16	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 8.1. Comparison 8 Agent: Isepamicin versus Amikacin, Outcome 1 Persistent bacteriuria.

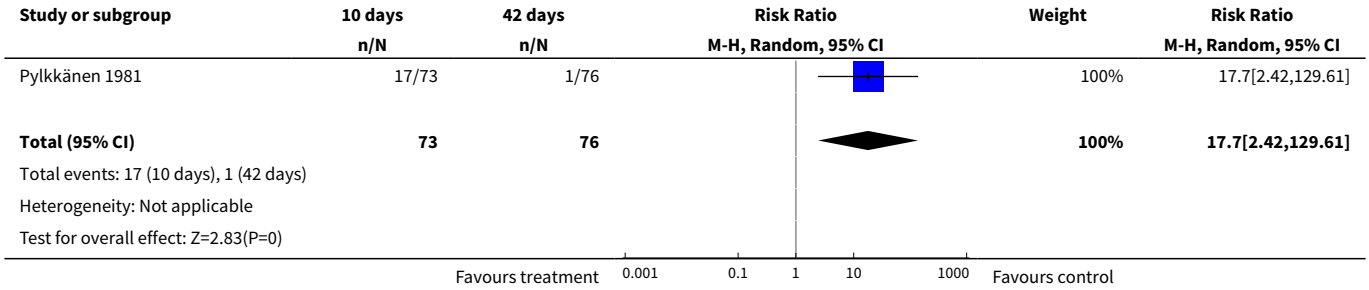




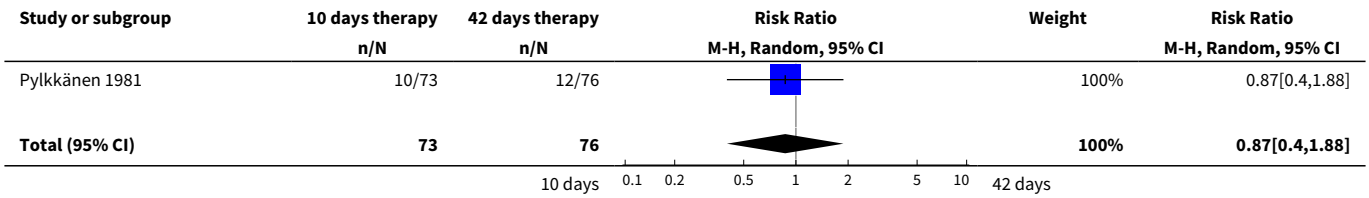
Comparison 9. Duration: 10 days versus 42 days of oral sulfafurazole

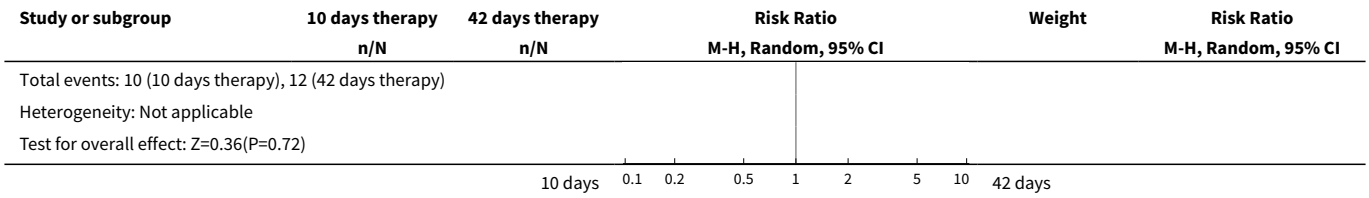
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent UTI within 1 month after ceasing therapy	1	149	Risk Ratio (M-H, Random, 95% CI)	17.70 [2.42, 129.61]
2 Recurrent UTI at 1-12 months after completing therapy	1	149	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.40, 1.88]

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



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

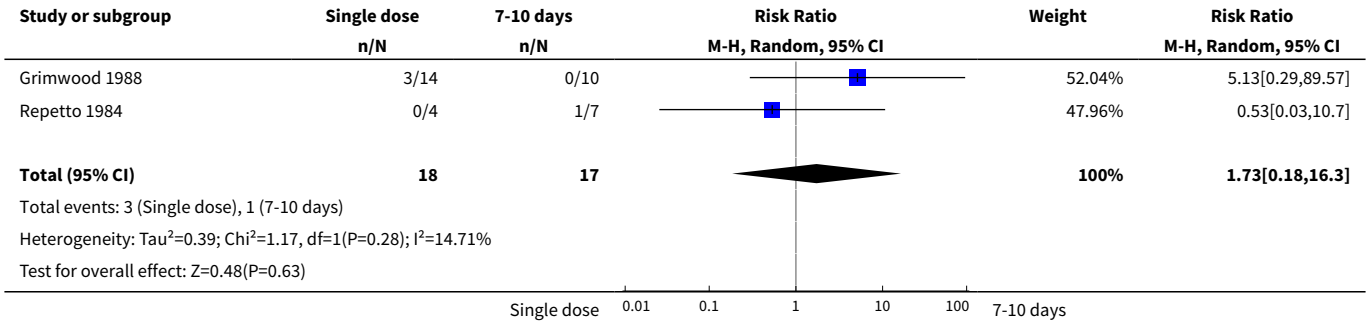




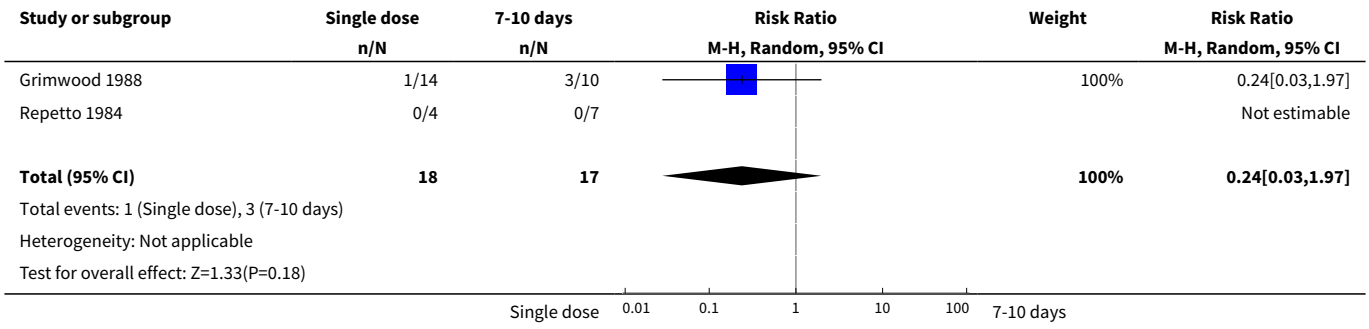
Comparison 10. Duration: single dose of parenteral antibiotic versus 7-10 days oral therapy

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 Duration: 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 Duration: single dose of parenteral antibiotic versus 7-10 days oral therapy, Outcome 2 UTI relapse or reinfection within 6 weeks.



ADDITIONAL TABLES

Table 1. Electronic seatch 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

Table 2. Methodological quality of included studies

Study ID	Allocation concealed	Blinding: patients	Blinding: clinicians	Blinding: outcomes	Intention to treat	N included/evaluated	Lost to follow up
Baker 2001	Adequate	No	No	Yes	No	77/69	5%
Bakkaloglu 1996	Unclear	No	No	Not stated	Not stated	100/100	0%
Benador 2001	Adequate	No	No	Yes	No	229/220	4%
Carapetis 2001	Adequate	No	No	Yes	Yes	179/179	0%
Fischbach 1989	Unclear	No	No	Not stated	Not stated	20/20	0%
Francois 1997	Adequate	No	No	Not stated	No	147/128	0%
Grimwood 1988	Unclear	No	No	Not stated	Not stated	69/24	0%
Hoberman 1999	Adequate	No	No	Yes	Yes	306/306	11%
Kafetzis 2000	Unclear	Not stated	Not stated	Not stated	Not stated	16/16	0%
Levtchenko 2001	Unclear	No	No	Yes	No	92/87	3%
Pylkkanen 1981	Unclear	No	No	Not stated	No	221/149	0%
Repetto 1984	Unclear	No	No	Not stated	Not stated	37/11	0%
Schaad 1998	Adequate	No	No	Yes	No	299/235	0.3%
Toporovski 1992	Unclear	No	No	Not stated	Not stated	37/37	0%
Vigano 1992	Unclear	No	No	Not stated	No	150/144	0%
Vilaichone 2001	Unclear	No	No	Not stated	Not stated	36/36	0%
Chong 2003	Unclear	No	No	Not stated	No	210/172	0%
Montini 2003	Unclear	No	No	Not stated	Not stated	387/387	Not stated

WHAT'S NEW

Date	Event	Description
10 May 2017	Amended	Converted to new review format.

HISTORY

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

Date	Event	Description
11 November 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Designing the Review; PB and EH with Cochrane Renal Group guidelines
Coordinating the review; PB and EH
Data Collection for the review was carried out independently by PB and EH, and included the following components:
Developing search strategy
Undertaking searches
Screening search results
Organising retrieval of papers
Screening retrieved papers against inclusion criteria
Appraising quality of papers
Abstracting data from papers (Renal Group data extraction form)
Searching for additional data in unpublished studies
Data management for the review
Entering data into RevMan; PB and EH
Analysis of data; PB and EH
Interpretation of data: PB and EH
Providing a methodological perspective
Providing a clinical perspective
Providing a policy perspective
Providing a consumer perspective
Writing the review; PB and EH
Providing general advice on the review; EH and JC
Securing the funding for the review; No funding required

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Australian Kidney Foundation, Australia.
- National Health and Medical Research Council, Australia.
- Commonwealth Department of Health and Aging, Australia.

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