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Modes of administration of antibiotics for symptomatic severe urinary tract infections.

Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003237.

DOI: [10.1002/14651858.CD003237.pub2](https://doi.org/10.1002/14651858.CD003237.pub2).

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Modes of administration of antibiotics for symptomatic severe urinary tract infections (Review)

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[Intervention Review]

Modes of administration of antibiotics for symptomatic severe urinary tract infections

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Editorial group: Cochrane Kidney and Transplant Group

Publication status and date: Edited (no change to conclusions), published in Issue 7, 2014.

Citation: Pohl A. Modes of administration of antibiotics for symptomatic severe urinary tract infections. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD003237. DOI: [10.1002/14651858.CD003237.pub2](https://doi.org/10.1002/14651858.CD003237.pub2).

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ABSTRACT

Background

Urinary tract infection (UTI), worldwide, is a major source of disease in children and adults. As it may have long-term consequences such as kidney failure and hypertension, it is important to treat patients with UTI adequately. Although standard management of severe UTI usually means intravenous (IV) therapy, at least initially, there are studies showing that oral therapy may also be effective.

Objectives

To assess whether the mode of administration of antibiotic therapy for severe UTI has an effect on cure rate, reinfection rate and kidney scarring.

Search methods

The Cochrane Renal Group's specialised register, the Cochrane Central Register of Controlled Trials (CENTRAL, in *The Cochrane Library*), MEDLINE and EMBASE were searched. No language restriction was applied. Reference lists of relevant articles and reviews were checked for additional studies and authors of relevant articles/abstracts were contacted for further information.

Selection criteria

All randomised controlled trials (RCTs) comparing different modes of antibiotic application for patients with severe UTI (children and adults) were considered.

Data collection and analysis

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

Main results

Fifteen RCTs (1743 patients) were included. Studies compared oral versus parenteral treatment (1), oral versus switch treatment (initial intravenous (IV) or intramuscular (IM) therapy followed by oral therapy) (5), switch versus parenteral treatment (6) and single dose parenteral followed by oral therapy versus oral (1) or switch therapy (3). There was a variety of short-term and long-term outcomes, but no pooled outcomes showed significant differences. Most included studies were small though and there were few outcomes for combination in a meta-analysis.

Authors' conclusions

There is no evidence suggesting that oral antibiotic therapy is less effective for treatment of severe UTI than parenteral or initial parenteral therapy. The results of this review suggest that the mode of application does not determine therapeutic success.

PLAIN LANGUAGE SUMMARY**No evidence that oral antibiotic therapy is less effective for treating urinary tract infection than intravenous antibiotics**

Severe urinary tract infection (UTI) is a common infection in adults and children, causing acute disease with a variety of symptoms such as fever and flank pain. This may lead to kidney damage, kidney failure or hypertension. Standard therapy involves antibiotics given at least initially by injection. This review identified 15 studies (1743 participants). The results of this review suggest oral therapy is equally effective in treating UTI and preventing long-term damage. This might reduce costs but also inconvenience for the patient.

BACKGROUND

Urinary tract infection (UTI) is a major source of disease with an estimated 150 million patients/year worldwide, costing the global economy more than six billion US dollars (Gonzalez 1999). It is a condition that causes substantial suffering for the patient and, especially if not treated properly, may - in extreme cases - cause substantial kidney scarring. It is thought that this might have long-term consequences such as progressive kidney failure and the development of hypertension (Ransley 1981; Smellie 1994). It is therefore important to diagnose early and treat patients with acute UTI adequately.

As many as 80% to 90% of symptomatic UTIs are caused by *Escherichia coli* (Winberg 1974; Orenstein 1999). Infections can be classified into (1) infection involving the kidney parenchyma (acute pyelonephritis) and (2) infections limited to the lower urinary tract. Ten to 20% of the symptomatic infections cannot be classified, and for practical reasons all patients with severe, symptomatic UTI are best treated as having kidney infection (Hansson 1999). Standard management of severe UTI recommends hospitalisation and therapy with intravenous (IV) antibiotics (Kunin 1994; McCracken 1989; Stamm 1993). However, oral therapy or initial IV therapy followed by oral therapy after cessation of fever would reduce costs, if it was shown to be effective in treating the infection and preventing complications. There are studies showing that oral therapy might be as effective in treating severe UTI as parenteral therapy, whereas other authors state that only parenteral therapy is feasible. In a recent survey about management and treatment of children with suspected acute pyelonephritis, 30% of all responding Belgian paediatricians considered oral treatment, the others recommended IV therapy (Levtchenko 2001). This heterogeneity in treatment strategies underlines the need for further assessment in regard to drug administration routes in patients with severe UTI.

OBJECTIVES

The aim of this review was to assess whether the application mode of an antibiotic therapy applied for severe UTI has an effect on outcomes such as cure rate, reinfection rate and kidney scarring.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) that compared one of the specified types of intervention for treatment of symptomatic severe UTI were included. Where studies included patients with other infections (e.g. pneumonia, sepsis), studies were included if results for therapy of UTI could be extracted separately.

Types of participants

The aim of this review was to analyse whether the application mode of antibiotic drugs has an effect on the outcome of severe UTI. One of the most problematic issues was to define severe UTI and thereby the participants to be included. Anatomically, UTIs can be classified into lower and upper UTI and whereas lower UTI can usually be treated with oral antibiotics, there is much controversy about therapy for upper UTI. There is no evident clinical distinction between the two entities.

For the purpose of this review, severe symptomatic UTI was defined as the clinical syndrome of fever, bacteriuria, pyuria and - beyond infancy - symptoms of UTI (flank pain, dysuria) and patients with severe symptomatic UTI, supposedly pyelonephritis, were included. Studies that included only patients with mild UTI (cystitis) were excluded. Complicated UTI was defined as UTI in patients with pre-existing complicating kidney disease such as obstruction, neurogenic bladder, chronic catheterisation.

Studies that included only patients with complicated UTI were excluded under the assumption that the underlying bacterial spectrum is different to that of uncomplicated severe UTI. Under the same assumption, studies that included only patients with nosocomially acquired UTI were also excluded. However, studies were not required to specifically exclude patients with urinary tract anomalies and studies that also included patients with complicated infections were included. Especially in paediatric studies, it was not obvious before infection whether a patient had a urinary tract anomaly and therefore if they had a complicated or uncomplicated UTI. There was no age or sex restriction.

Types of interventions

1. Oral versus parenteral (defined as IV or intramuscular (IM)) antibiotic therapy for the total duration of the therapy.
2. Oral versus switch therapy, defined as initial parenteral treatment with subsequent oral antibiotic treatment.
3. Switch therapy versus parenteral therapy total duration of the therapy.
4. Single shot parenteral therapy (initial IM dose) followed by oral therapy versus oral therapy.
5. Single shot parenteral therapy (initial IM dose) followed by oral therapy versus switch therapy.

Studies comparing IM versus IV therapy (i.e. two parenteral treatment modes) were excluded.

Types of outcome measures

1. Cure rates (defined as no clinical signs, bacteriological cure rate defined as eradication of bacteria, combined clinical and bacteriological cure rate defined as no clinical signs and eradication of bacteria): a) under therapy, b) at end of therapy, and c) after an interval.
2. Reinfection rate (defined as new pathogen in urine culture): a) at end of therapy, and b) after an interval (length of interval varied in the included studies).
3. Relapse rate (defined as initial pathogen in urine culture after it had been eradicated): a) at end of therapy, and b) after an interval (length of interval varied in the included studies).
4. Number of patients with fever after 48 hours.
5. Number of patients with kidney scarring (DMSA scan) after six months.
6. Adverse events.
7. Time to cessation of fever.
8. Time of clinical symptoms.

Search methods for identification of studies

Relevant studies were identified by searching electronic databases (Appendix 1 *Electronic search strategies*) and other resources:

- Cochrane Renal Group's specialised register.
- Cochrane Central Register of Controlled Trials (CENTRAL in *The Cochrane Library*, Issue 2, 2007).

CENTRAL and the Cochrane Renal Group's specialised register contain the handsearched results of conference proceedings from general and speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective ([Master List 2007](#)). Please refer to The Cochrane Renal Review Group's Module in *The Cochrane Library* for the complete list of nephrology conference proceedings searched.

- MEDLINE (from 1966 to June 2007): the search strategy incorporated the Cochrane highly sensitive search strategy for identifying RCTs in MEDLINE ([Dickersin 1994](#)).
- EMBASE (from 1980 to June 2007): the search strategy incorporated a sensitive strategy for identifying RCTs in EMBASE ([Lefebvre 1996](#)).
- Reference lists of identified studies and major reviews.
- Contact with researchers active in the field and primary authors of identified relevant studies for details of unpublished studies.

No language restrictions were applied. Letters, abstracts, and unpublished studies were accepted to reduce publication bias. If duplicate publication was suspected, authors were contacted for clarification, and if confirmed, the publication with the most and/or the longest follow-up data was used for the review.

Data collection and analysis

The search strategy as described above was performed by one author (AP) with the help of a librarian. Titles and abstracts were screened and if necessary, the full text was assessed. Studies reported in non-English language were translated before assessment. In case of unclear presentation or incomplete data, information was sought from the original author by written correspondence or in one case ([Hoberman 1999](#)) by telephone. From two studies ([Montini 2007](#); [Neuhaus 2008](#)), only incomplete data was included. These studies are completed but not as yet published.

Data was extracted using standard data extraction sheets as provided by the Cochrane Renal Group. The quality of the studies was assessed without blinding to authorship. The items assessed were allocation concealment, blinding, drop out rate and use of intent-to-treat analysis. Allocation concealment was classified as "adequate" in case of a randomisation method that would not allow the investigator or the patient to know or influence to which intervention group the patient was enrolled before the actual begin of the study. If there was no further information about method of randomisation, it was classified as "unclear". There were no studies with openly inadequate allocation concealment. Blinding was divided into blinding of patients, clinicians and outcome assessors. Dropout rate lists the percentage of patients lost to follow-up or with no data for the primary outcome measure. In order to be classified as intention-to-treat analysis, study assessment had to confirm that all randomised patients were analysed according to randomisation schedule.

For statistical analysis dichotomous outcomes were expressed as risk ratio (RR) with a 95% confidence interval (CI). For continuous outcomes (time to cessation of fever and time of clinical symptoms), the mean difference (MD) was used, also with a 95% CI.

In both cases, data were pooled using the random effects model, but the fixed effects model was also applied in order to control the robustness of the analysis. Heterogeneity was assessed using a Chi-square statistic with an alpha of 0.1 for statistical significance, and also the I^2 statistic ([Higgins 2003](#)). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

There were insufficient studies to examine publication bias.

RESULTS

Description of studies

Over 2,000 titles and abstracts were identified and screened. Fifty reports were identified as potentially relevant and full text versions were obtained, 34 studies were subsequently excluded (for details see [Characteristics of excluded studies](#)).

The remaining 15 studies (16 reports, 1743 participants) fulfilled the inclusion criteria and were included in this review. The authors of six studies were contacted for further information ([Gok 2001](#); [Hoberman 1999](#); [Mombelli 1999](#); [Montini 2007](#); [Neuhaus 2008](#); [Noorbakhsh 2004](#)), five authors replied ([Hoberman 1999](#); [Mombelli 1999](#); [Montini 2007](#); [Neuhaus 2008](#); [Noorbakhsh 2004](#)). For two studies ([Montini 2007](#); [Neuhaus 2008](#)), only preliminary data was included, the studies have been completed but are as yet unpublished. Studies were conducted in eight countries (USA, France, Switzerland, Turkey, Iran, Italy, Spain and Thailand) and published in English, French, Italian and German. Studies were published between 1989 and 2007.

Participants

Nine studies recruited children in different age groups ([Baker 2001](#); [Fischbach 1989](#); [Francois 1997](#); [Gok 2001](#); [Hoberman 1999](#); [Montini 2007](#); [Neuhaus 2008](#); [Noorbakhsh 2004](#); [Vilaichone 2001](#)), among these, six studies including children less than one year of age ([Baker 2001](#); [Francois 1997](#); [Hoberman 1999](#); [Montini 2007](#); [Neuhaus 2008](#); [Vilaichone 2001](#)) and [Noorbakhsh 2004](#) did not specify the lower age boundary. Of the remaining six studies, [Sanchez 2002](#) only included women and [Millar 1995](#) only included pregnant women.

The objective of this review was to compare different application modes of antibiotics in severe UTI, which means patients with pyelonephritis rather than cystitis. Clinically, it is not always easy to distinguish between these entities, especially in small children. Therefore, the definition of UTI varied in different studies. All studies required clinical signs and symptoms of UTI and a positive urinalysis. In all but two studies, a positive urine culture before treatment was a prerequisite. [Millar 1995](#) did not exclude patients with a negative urine culture (one each group) or without pretreatment culture (nine patients) if the clinical signs and symptoms were strongly indicative of pyelonephritis. In [Mombelli 1999](#), two patients in each group had received antibiotics 24 hours before collection of urine culture and, although their urine cultures were negative, they were included. Severity of UTI was defined differently. Most studies used fever as a sign of severity, other studies also required laboratory values (elevated CRP, leucocytosis) ([Fischbach 1989](#); [Francois 1997](#); [Mombelli 1999](#); [Montini 2007](#); [Neuhaus 2008](#)) or specified that the clinical condition "had to require parenteral antibiotics" ([Childs 1990](#)). Symptoms of UTI and positive urinalysis were not always further defined and the method of urine collection was only described in seven studies ([Baker 2001](#); [Gok 2001](#); [Hoberman 1999](#); [Mombelli 1999](#); [Neuhaus 2008](#); [Sanchez](#)

2002; Vilaichone 2001). In seven studies (Baker 2001; Francois 1997; Hoberman 1999; Millar 1995; Montini 2007; Sanchez 2002; Vilaichone 2001), patients with known urologic anomalies were excluded, whereas in six studies, patients with complicated UTI were included (Childs 1990; Fischbach 1989; Gok 2001; Mombelli 1999; Puppo 1989; Regnier 1989). Studies that only and explicitly included patients with complicated UTI were excluded from this review.

Interventions

- Six studies analysed switch therapy (IV therapy initially followed by oral antibiotic therapy) versus parenteral (IV or IM) therapy in UTI (Childs 1990; Fischbach 1989; Francois 1997; Noorbakhsh 2004; Regnier 1989; Vilaichone 2001). The IV antibiotics used were cefotaxime, amoxicillin/clavulanic acid, ceftriaxone, ceftazidime, ciprofloxacin, netilmicin, amikacin and gentamicin. The oral antibiotics used were ciprofloxacin, amoxicillin/clavulanic acid, cefixime or cefibuten. Duration in the two treatment groups was usually equivalent and varied between 4 to 14 days.
- Five studies compared oral versus switch therapy (Gok 2001; Hoberman 1999; Mombelli 1999; Montini 2007; Neuhaus 2008), using cefibuten, cefixime, amoxicillin/clavulanic acid and ciprofloxacin as oral antibiotics and ceftriaxone, cefotaxime, ciprofloxacin and ceftizoxime as IV or IM therapy. One study (Mombelli 1999) did not specify duration of therapy, and all other studies treated between 10 and 14 days.
- One study assessed oral versus parenteral therapy (Puppo 1989) using norfloxacin as oral therapy for seven days and aztreonam as parenteral therapy.
- Two studies used single shot parenteral therapy (IM or IV) followed by oral therapy versus switch therapy (Millar 1995; Sanchez 2002). Antibiotics used were ceftriaxone and cefazolin as parenteral drugs and cephalexin and cefixime applied orally, treatment duration was 10 days.
- One study compared single dose parenteral (IM) therapy followed by oral therapy versus oral therapy (Baker 2001) using ceftriaxone as IM and trimethoprim-sulfamethoxazole as oral agent for 10 days.

Outcomes

Outcomes varied in the different studies, so it was not always feasible to combine results. Even the primary outcome (cure rate) was defined differently. Cure rates were presented as clinical or bacteriological or combined clinical and bacteriological cure rates, outcome was assessed during therapy or at end of therapy or after an interval of several weeks. Only nine studies presented adverse events (Baker 2001; Fischbach 1989; Francois 1997; Millar 1995; Mombelli 1999; Neuhaus 2008; Regnier 1989; Sanchez 2002; Vilaichone 2001).

Further study characteristics are presented in the table - *Characteristics of included studies*.

Risk of bias in included studies

Only RCTs were included (see Table 1- *Methodological quality of included studies*).

Allocation concealment

There were eight studies with adequate allocation concealment (Baker 2001; Childs 1990; Francois 1997; Hoberman 1999; Millar 1995; Mombelli 1999; Montini 2007; Neuhaus 2008) and seven studies with unclear (Fischbach 1989; Gok 2001; Noorbakhsh 2004; Puppo 1989; Regnier 1989; Sanchez 2002; Vilaichone 2001). No correlation between date of publication and allocation concealment could be revealed.

Blinding

Blinding of patients would only have been feasible with a double dummy design and therefore none of the studies blinded patients. Only Baker 2001 concealed the mode of antibiotic application from the treating clinicians. In six studies, outcome assessors were blinded (Baker 2001; Hoberman 1999; Millar 1995; Mombelli 1999; Neuhaus 2008; Noorbakhsh 2004). In the remaining studies, there was no information about blinding.

Intention-to-treat

Only three studies analysed results on an intention-to-treat basis (Hoberman 1999; Millar 1995; Vilaichone 2001) and it was unclear in four studies (Fischbach 1989; Gok 2001; Montini 2007; Puppo 1989).

Dropout rates

Six studies had a dropout rate of more than 10% (Childs 1990; Francois 1997; Hoberman 1999; Millar 1995; Neuhaus 2008; Regnier 1989).

Effects of interventions

Due to different outcome parameters, few studies were available for combination in a meta-analysis. The results were the same in a fixed effects model or a random effects model, therefore only the results of the random effects model are reported.

Switch versus parenteral therapy

Six studies (373 patients) compared switch versus parenteral therapy. In all outcomes there was no significant difference between switch and parenteral therapy.

- The number of patients with fever after 48 hours was not significantly different between the two groups (Analysis 1.1 (1 study, 20 patients): RR 5.00, 95% CI 0.27 to 92.62).
- Under therapy, there was no significant difference in bacterial eradication (Analysis 1.2 (1 study, 19 patients): RR 0.79, 95% CI 0.54 to 1.15).
- At the end of therapy, there was no statistical difference in clinical cure (Analysis 1.3 (2 studies, 137 patients): RR 1.01, 95% CI 0.94 to 1.10, $I^2 = 0\%$) or bacteriological cure (i.e. bacterial eradication) (Analysis 1.4 (2 studies, 76 patients): RR 1.11, 95% CI 0.90 to 1.36, I^2 not applicable). The combined outcome, clinical and bacteriological cure at the end of therapy, was also not significantly different (Analysis 1.5 (4 studies, 294 patients): RR 0.99, 95% CI 0.94 to 1.04, $I^2 = 4.3\%$).
- At the end of therapy (Analysis 1.6) and after an interval (Analysis 1.9), the rate of reinfection was not statistically different (Analysis 1.6 (1 study, 72 patients): RR 1.00, 95% CI 0.15 to 6.72; Analysis 1.9 (4 studies, 239 patients): RR 0.76, 95% CI 0.30 to 1.90, $I^2 = 0\%$).

- The number of patients with clinical and bacteriological cure after an interval was not statistically different. There was some heterogeneity ([Analysis 1.7](#) (3 studies, 219 patients): RR 0.99, 95% CI 0.89 to 1.11, $I^2 = 39.0\%$). Subgroup analysis showed that for the paediatric studies clinical and bacteriological cure was ([Analysis 1.7.1](#) (2 studies, 138 patients): RR 1.03, 95% CI 0.96 to 1.10, $I^2 = 5.9\%$) and for the adult study ([Analysis 1.7.2](#) (1 study, 81 patients): RR 0.92, 95% CI 0.73 to 1.16). Age was not the only distinguishing factor between the paediatric studies and the adult study. In the paediatric studies, the outcome was assessed 10 to 20 days ([Franco 1997](#)) or 14 days after stopping therapy ([Vilaichone 2001](#)) compared to 10 to 84 days in the adult study ([Regnier 1989](#)).
- The relapse rate was not significantly different ([Analysis 1.8](#) (3 studies, 203 patients): RR 2.79, 95% CI 0.30 to 25.67, I^2 not applicable).
- Kidney scarring on DMSA scan after six months did not differ significantly ([Analysis 1.10](#) (1 study, 36 patients): RR 0.92, 95% CI 0.56 to 1.50).
- The number of patients with adverse events was statistically the same ([Analysis 1.11](#) (4 studies, 292 patients): RR 0.85, 95% CI 0.19 to 3.83, $I^2 = 44.8\%$). There were only minor side effects, mainly gastrointestinal upsets. There was moderate heterogeneity. Subgroup analysis showed that this heterogeneity might be explained by age. The paediatric studies had a RR of 0.67 (95% CI 0.30 to 1.53, $I^2 = 0\%$) and the adult study had an RR of 0.85 (95% CI 0.19 to 3.83).

Switch versus oral therapy

Five studies (1040 patients) compared switch therapy with oral therapy. Two of these studies were included with preliminary data only ([Montini 2007](#); [Neuhaus 2008](#)), they are both still awaiting publication. There was no significant difference between switch and oral therapy for all outcomes.

- Under therapy ([Analysis 2.1](#)), at the end of therapy ([Analysis 2.2](#)) and after an interval ([Analysis 2.5](#)), the number of patients with clinical and bacteriological cure was not statistically different ([Analysis 2.1](#) (3 studies, 599 patients): RR 1.04, 95% CI 0.97 to 1.12, I^2 not applicable; [Analysis 2.2](#) (1 study, 54 patients): RR 0.94, 95% CI 0.78 to 1.13; [Analysis 2.5](#) (3 studies, 493 patients): RR 0.97, 95% CI 0.93 to 1.01, $I^2 = 0\%$).
- The rate of reinfection at the end of therapy ([Analysis 2.3](#)) and after an interval ([Analysis 2.6.1](#), [Analysis 2.6.2](#)) did not differ statistically ([Analysis 2.3](#) (1 study, 54 patients): RR 1.16, 95% CI 0.18 to 7.64; [Analysis 2.6.1](#) (symptomatic reinfection, 1 study, 187 patients): RR 0.67, 95% CI 0.27 to 1.67; [Analysis 2.6.2](#) (symptomatic and asymptomatic reinfection, 2 studies, 341 patients): RR 0.64, 95% CI 0.29 to 1.42, $I^2 = 0\%$).
- There was no significant difference in the number of patients with relapse at the end of therapy ([Analysis 2.4](#)) or after an interval ([Analysis 2.7](#)) ([Analysis 2.4](#) (1 study, 54 patients): RR 0.23, 95% CI 0.01 to 4.59; [Analysis 2.7](#) (1 study, 54 patients): RR 5.77, 95% CI 0.29 to 114.79).
- Kidney scarring on DMSA scan after six months did not differ significantly ([Analysis 2.8](#) (2 studies, 424 patients): RR 0.87, 95% CI 0.35 to 2.16, $I^2 = 77.8\%$). There was substantial heterogeneity among the two combined studies. In [Neuhaus 2008](#) only 152/365 of the initially randomised patients contribute to the outcome. There is no final adjusted analysis available and therefore

the preliminary data might be confounded. According to the author, there was no significant difference between treatment groups after adjustment for size of the initial kidney lesion. The DMSA scan results for [Montini 2007](#) are not available yet, but preliminary data showed that of the 90 scans available at the 1 year follow-up, 29% had scars with an equal proportion in the two treatment arms.

- Mean time to cessation of fever did not differ significantly ([Analysis 2.9](#) (3 studies, 834 patients): MD 0.40, 95% CI -2.94 to 3.74, $I^2 = 17.4\%$).
- The adverse events rate was not different between the two groups ([Analysis 2.10](#) (2 studies, 506 patients): RR 0.96, 95% CI 0.06 to 15.02, I^2 not applicable).

Oral versus parenteral therapy

One study ([Puppo 1989](#)) compared oral versus parenteral therapy using norfloxacin as oral therapy. Patients with cystitis and pyelonephritis were included in the study, but only the latter were included in this review. Parenteral therapy had a significantly better outcome than oral therapy in both outcomes. For patients with cystitis, no difference could be detected with high cure rates in both groups.

- The number of patients with bacteriological cure at the end of therapy was significantly higher in the parenteral group compared to the oral group ([Analysis 3.1](#) (1 study, 38 patients): RR 1.37, 95% CI 1.02 to 1.84). This became even more evident after an interval ([Analysis 3.2](#) (1 study, 38 patients): RR 1.95, 95% CI 1.24 to 3.08).

Switch versus single shot therapy

Two studies ([Millar 1995](#); [Sanchez 2002](#)) compared switch versus single shot therapy. Only two outcomes (number of patients with clinical cure under therapy and number of patients with adverse events) could be combined. There was no significant difference between both modes of application.

- The number of patients with clinical cure under therapy was not significantly different ([Analysis 4.1](#) (2 studies, 225 patients): RR 0.93, 95% CI 0.86 to 1.02, $I^2 = 30.8\%$). At the end of therapy, all patients were clinically cured.
- All patients showed bacterial eradication under therapy. At the end of therapy, there was no statistical difference in bacterial eradication ([Analysis 4.6](#) (1 study, 110 patients): RR 0.96, 95% CI 0.79 to 1.16).
- The mean time to cessation of fever ([Analysis 4.3](#)) and mean duration of clinical symptoms ([Analysis 4.4](#)) were not significantly different ([Analysis 4.3](#) (1 study, 105 patients): MD 0.10, 95% CI -0.19 to 0.39; [Analysis 4.4](#) (1 study, 105 patients): MD 0.30, 95% CI -0.16 to 0.76).
- The adverse events rate was not statistically different ([Analysis 4.7](#) (2 studies, 225 patients): RR 4.00, 95% CI 0.46-34.75, I^2 not applicable).

Single shot versus oral therapy

One study ([Baker 2001](#)) compared single shot IM followed by oral therapy versus oral therapy. All outcomes showed no significant difference between the two groups.

- There was no statistical difference in the number of patients with clinical and bacteriological cure under therapy ([Analysis 5.1](#) (1 study, 69 patients): RR 0.97, 95% CI 0.81 to 1.17).
- The number of patients with bacteriological cure under therapy was not statistically different ([Analysis 5.2](#) (1 study, 69 patients): RR 0.97, 95% CI 0.83 to 1.14).
- There was no patient with a reinfection after an interval in either group.
- The adverse events rate was not statistically different ([Analysis 5.4](#) (1 study, 69 patients): RR 1.37, 95% CI 0.33 to 5.68).

DISCUSSION

Although severe UTI is usually treated exclusively with IV antibiotics (or at least initially) followed by oral antibiotics, this review suggests that the mode of application is not essential for the success of therapy. All comparisons of different application modes did not show a significant difference in the various outcomes analysed. The available oral antibiotics (especially third generation cephalosporins) seem to be potent enough to treat patients with pyelonephritis efficiently. Even long term outcomes such as kidney scarring do not seem to differ.

There is however insufficient evidence comparing oral versus parenteral therapy. Only one study was found, and only part of the data could be used as the study also included patients with mild/lower UTI ([Puppo 1989](#)). This study found that oral therapy with norfloxacin was significantly less successful than parenteral therapy. According to this study, norfloxacin cannot be recommended as therapy for severe upper UTI. Ciprofloxacin, another fluoroquinolone, showed the same results when comparing oral and switch therapy.

When comparing switch and parenteral therapy, there was some heterogeneity in 1/11 outcomes ([Analysis 1.7](#)). The interpretation of this heterogeneity was difficult because in there was only often only one or two studies for each meta-analysis. Nevertheless, subgroup analysis showed either age or timing of outcome assessment (2 weeks versus up to 84 days) could explain this heterogeneity.

There was also substantial heterogeneity in the comparison of switch versus oral therapy involving two studies. [Neuhaus 2008](#) included only preliminary data, there is as yet no final adjusted analysis available and therefore the preliminary data might be confounded. According to the author, there was no significant difference between treatment groups after adjustment for size of the initial kidney lesion. The DMSA scan results from [Montini 2007](#) are not available as yet, but preliminary data showed that of the 90 scans available at the 1 year follow-up, 29% had scars with an equal proportion in the two treatment arms. Therefore, at this point there is no conclusive evidence showing whether switch or oral therapy are equally effective or one is superior to the other.

Most included studies were of small sample size, many were of suboptimal quality. Studies were not designed as equivalence studies but rather they aimed to determine whether there were differences between two treatments. Failure to show a difference

in an RCT does not necessarily mean that two treatments are equivalent ([Jones 1996](#)). There were few outcomes that could be combined in a meta-analysis and as previously stated some evidence is still awaiting publication ([Montini 2007](#); [Neuhaus 2008](#)). Cure rates were high and, when reported, adverse events were uncommon, so that the fact that no statistical difference was found might not hold true for larger populations.

There was no evidence available concerning long-term outcomes other than kidney scarring. Information on long-term outcomes that are clinically more relevant is missing in all studies.

As long as there is no evidence suggesting that oral therapy is inferior to parenteral therapy or partially parenteral therapy, oral therapy might be used for treating patients with UTI. This would reduce the inconvenience of parenteral application especially in children. It might also help to reduce costs (and again inconvenience) by shortening the number of hospital days. Nevertheless, if treating with oral antibiotics, patients have to be supervised carefully to guarantee a good compliance and also to identify patients not tolerating oral drugs. In most studies, only patients tolerating oral therapy were included, and for children with pyelonephritis oral intake is often not possible in the beginning due to gastrointestinal upsets. Therefore, compliance and tolerance could impact greatly on efficacy and effectiveness. In addition, some oral antibiotics, such as third generation cephalosporins, are usually more expensive than many IV drugs. Therefore a proper cost-effectiveness analysis still has done to show that reduced days of hospitalisation outweighs drug costs.

AUTHORS' CONCLUSIONS

Implications for practice

This review has not shown that any mode of application of antibiotic therapy in severe UTI is superior to another. All included studies were small and not designed as equivalence studies. As long as there is no evidence suggesting that oral therapy is inferior to parenteral therapy, it might be justified to treat patients orally, at least in patients tolerating the oral pathway, because of less inconvenience for the patient and eventually less cost. When choosing oral antibiotics, third generation cephalosporins should be preferred, whereas there is weak evidence that norfloxacin should not be used when treating severe UTI.

Implications for research

For the evaluation of long-term outcomes such as kidney scarring on DMSA scans, more studies are needed and the complete publication of the studies by [Montini 2007](#) and [Neuhaus 2008](#) are awaited.

ACKNOWLEDGEMENTS

Thank you to Mrs Edith Motschall for her assistance with the search strategy, Dr Gerd Antes and Prof Johannes Forster for their advice during the preparation of the protocol, and Drs Suzanne Geerlings, Vladimir Rafalsky and Thomas Welch for their editorial advice during the preparation of this review.

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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	Prospective RCT at a tertiary care centre. No central randomisation. Opaque envelopes blindly selected from bin, clinicians blinded.
Participants	INCLUSION CRITERIA Number: 34 (group 1), 35 (group 2). Gender (F/total): 32/34 (group 1), 30/35 (group 2). Age: 6 months to 12 years. Fever > 38.0°C, history and physical examination suggesting UTI and positive urine culture from catheter specimen or MSU. EXCLUSION CRITERIA Abnormality of urinary tract, already taking antibiotics, allergy to study medication.
Interventions	TREATMENT GROUP 1 Single shot IM /oral therapy. Ceftriaxone IM 50 mg/kg once initially followed by oral trimethoprim 10 mg/kg/d for 10 days. TREATMENT GROUP 2 Oral therapy.

Modes of administration of antibiotics for symptomatic severe urinary tract infections (Review)

Baker 2001 (Continued)

Trimethoprim 10 mg/kg/d for 10 days.

Outcomes	1. Clinical and bacteriological cure after 48 hours. 2. Bacteriological cure rate after 48 hours. 3. Reinfection after interval of 1 month (n, %) 4. Relapse rate after interval of 1 month (n, %). 5. Adverse events rate (n, %).
Notes	Of 95 patients who met the inclusion criteria, 87 were enrolled (6 gave no consent, 2 were not petitioned). Fourteen patients were excluded after randomisation because urine culture was negative. Three (group 1) and 1 (group 2) were lost to follow-up.

Risk of bias

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

Childs 1990

Methods	Prospective RCT. Computer-generated randomisation. No ITT.
Participants	INCLUSION CRITERIA Number: 19 (group 1), 21 (group 2). Gender (M/F): unknown. Age: > 18 years. Clinical symptoms of severe UTI requiring parenteral antibiotic therapy and a positive urine culture. EXCLUSION CRITERIA Cases of allergy, severe underlying disease, renal impairment, pregnancy, urinary tract obstruction, catheterization.
Interventions	GROUP 1 IV switch therapy. Ciprofloxacin 200 mg twice daily IV for 2 to 5 days, followed by 500 mg twice daily orally for up to 14 days. GROUP 2 IV therapy. Ceftazidime 500 mg thrice daily for 4 to 9 days.
Outcomes	1. Clinical cure rate at end of therapy (clinical cure or improvement at end of therapy, bacteriologic eradication 5 to 9 days after therapy end). 2. Bacteriological cure rate at end of therapy (clinical cure or improvement at end of therapy, bacteriologic eradication 5 to 9 days after therapy end). 3. Reinfection rate at end of therapy.
Notes	Of 63 patients enrolled, 23 were excluded from evaluation because of missing/sterile urine culture before or after therapy (20), pathogen resistant to study drug (2) or renal impairment (1). Two patients in each group had acute prostatitis, 1 patient in IV group had epididymitis. Fifteen patients in each group were classified as having complicated UTI.

Risk of bias
Modes of administration of antibiotics for symptomatic severe urinary tract infections (Review)

Childs 1990 (Continued)

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

Fischbach 1989

Methods	Prospective RCT. Randomisation table. No information whether ITT.
Participants	INCLUSION CRITERIA Number: 10 (group 1), 10 (group 2). Age: children, age not stated. Gender (F/total): 8/10 (group 1), 7/10 (group 2). Less than 1 year with fever > 38.5°C, pyuria, bacteriuria, positive urine culture, ESR > 35 mm/h, elevated CRP and orosomucoid. EXCLUSION CRITERIA Beta lactam allergy, antibiotic therapy 72 hours before study inclusion, impaired renal function or post-op infection.
Interventions	GROUP 1 IV switch therapy. amoxicillin/clavulanate acid 100 mg/kg/d IV for 7 days followed by 50 mg/kg/d po for 7 days. GROUP 2 IV therapy. Cefotaxime 100 mg/kg/d IV for 14 days.
Outcomes	1. Number of patients with fever > 48 hours. 2. Number of patients with bacteriological cure after 48 hours. 3. Number of patients with reinfection after interval (7 days after end of therapy). 4. Number of patients with relapse after interval (7 days after end of therapy). 5. Number of patients with adverse events. 6. Lab parameter. 7. No treatment failure rate. 8. No clinical cure rate.
Notes	No patient flow diagram.

Risk of bias

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

Francois 1997

Methods	Prospective, multicentre RCT. Randomisation per telephone call (Minitel) at day 4. No ITT.

Francois 1997 (Continued)

Participants	INCLUSION CRITERIA Number: 63 (group 1), 65 (group 2). Age: 6 months to 10 years. Gender (F/total): 57/63 (group 1), 57/65 (group 2). Fever > 38.0°C, elevated CRP, pyuria, bacteriuria, positive urine culture with germ sensitive to ceftriax- on, netilmicin and cefixime. EXCLUSION CRITERIA Allergy to antibiotics, catheterization, complicated UTI, immune deficiency, kidney failure, urine cul- ture not sterile after 48 hours of treatment.
Interventions	GROUP 1 IV switch therapy. Ceftriaxon 50 mg/kg/d IV and netilmicin 6 to 7.5 mg/kg/d IV for 4 days followed by cefixime 8 mg/kg/d PO for 6 days. GROUP 2 IV/IM therapy. Ceftriaxon/netilmicin for 4 days followed by ceftriaxon 50 mg/kg/d IM or IV for 6 days. CO INTERVENTIONS Both groups received antibiotic prophylaxis for 20 days (nitroxoline).
Outcomes	1. Cure rate defined as no clinical signs and bacteriological eradication 48 hours after end of treatment (n, %) and after interval of 20 to 30 days. 2. Reinfection rate after interval (20 to 30 days) (n, %). 3. Adverse events rate (n, %).
Notes	Of 169 patients who met the inclusion criteria, 147 were randomised. Seven (group 1) and 12 (group 2) were excluded from analyses because there was no evaluable result.
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment (selection bias)	Low risk A - Adequate

Gok 2001

Methods	Prospective RCT at Paediatric University Hospital. No information on method of randomisation or type of analysis (ITT?)
Participants	INCLUSION CRITERIA Number: 25 (group 1), 29 (group 2). Age: 2 to 13 years, mean age 6.6 ± 3.3 years. Gender (F/total): 20/25 (group 1) 24/29 (group 2). Symptoms of UTI and pyuria, bacteriuria and positive urine culture (clean catch urine) without antibiot- ic prophylaxis.
Interventions	GROUP 1 Oral therapy. Cefixime 8 mg/kg/d for 10 days. GROUP 2 IM switch therapy. Ceftizoxime IM 50 mg/kg twice daily for 2 days followed by oral cefixime for 8 days.

Gok 2001 (Continued)

Outcomes	1. Cure rate: defined as resolution of all signs and symptoms and eradication of pathogen at end of treatment and after 3 weeks. 2. Reinfection rate: defined as development of new or worsened signs or symptoms and infection with a new pathogen in patients who had been cured at end of treatment and after 3 weeks. 3. Relapse: defined as eradication of baseline pathogen with reappearance of same pathogen at end of treatment and after 3 weeks.
Notes	Symptoms of UTI not further specified. No patient flow diagram. Adverse events: one patient developed diarrhoea caused by cefixime, but no information to which group this patient belonged.

Risk of bias

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

Hoberman 1999

Methods	Prospective, multicentre RCT. Computer-generated randomisation list. Stratification based on age and duration of fever. ITT.
Participants	INCLUSION CRITERIA Number: 153 in each group. Gender (F/total): 137/153 (group 1), 136/153 (group 2) Age: 1 to 24 months. Fever > 38.3°C, pyuria, bacteriuria and positive urine culture from catheter specimen. EXCLUSION CRITERIA Unequivocal source for fever, history of UTI or abnormality of urinary tract.
Interventions	GROUP 1 IV switch therapy. Cefotaxime IV 200 mg/kg/d for 3 days or until afebrile > 24 hours, followed by oral cefixime 8 mg/kg/d for 14 days. GROUP 2 Oral therapy. Cefixime 16 mg/kg/d initially followed by 8 mg/kg/d for 14 days.
Outcomes	1. Cessation of fever (hours, mean $\pm$ SD). 2. Cure rate defined as resolution of clinical signs and symptoms and sterilization of urine (obtained in 291/306 children) after 24 hours. 3. Reinfection rate after interval of 6 months (n, %). 4. DMSA renal scan after 0.5 year.
Notes	Three children were not randomised because they were deemed too sick. One child in the oral group was unable to tolerate oral drugs and was given IV drugs. Children between 4 to 8 weeks of age and children who needed IV drip were kept at hospital, but treated orally according to protocol.

Risk of bias

Hoberman 1999 (Continued)

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

Millar 1995

Methods	Prospective RCT at University hospital. Random number table used to create sealed, opaque envelopes, randomisation in blocks of 6, envelopes kept separately. ITT.
Participants	INCLUSION CRITERIA Number: 60 pregnant women in each group. Gestational week < 24 weeks, with fever > 38.4°C, flank pain, pyuria. EXCLUSION CRITERIA Sepsis, respiratory insufficiency, fever > 39.8°C, RR < 90/50 mm Hg, creatinine > 1.4 mg/dL, allergy to cephalosporins, inability to tolerate oral intake, serious medical illness, known renal or urologic problems, antibiotic therapy during 2 preceding weeks.
Interventions	GROUP 1 Single shot IM/oral therapy. Ceftriaxone 1 g IM twice within 18 to 36 hours, followed by cephalexin 500 mg PO 4 times/d for 10 days. GROUP 2 IV switch therapy. Cefazolin 1 g three times/d until afebrile for 48 hours, followed by cephalexin 500 mg PO 4 times/d for 10 days. CO INTERVENTIONS All patients received oral prophylaxis with nitrofurantoin till 6 weeks postpartum.
Outcomes	1. Clinical cure during first 3 days. 2. Bacterial cure at end of therapy. 3. Adverse events rate (minor and major combined).
Notes	Of 120 patients enrolled, 1 patient each group had negative urine culture at beginning, 9 patients had no urine culture at beginning, 2 patients of Group 1 were given IV therapy because of sepsis, but all were analysed according to randomisation nevertheless (ITT). Seven (group 1) and 3 (group 2) had no urine culture at end of therapy (of those, 3 were clinically doing well). Number of patients with clinical cure at end of therapy not clearly presented.

Risk of bias

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

Mombelli 1999

Methods	Prospective, multicentre RCT at 4 community care centres. Randomisation at each centre by sealed envelopes/code list.

Modes of administration of antibiotics for symptomatic severe urinary tract infections (Review)

Mombelli 1999 (Continued)

No ITT.

Participants	INCLUSION CRITERIA Number: 72 (group 1), 69 (group 2). Gender (F/total): (44/72 (group 1), 39/69 (group 2). Age: >18 years. Fever > 37.5°C, pyuria, bacteriuria, leukocytosis and signs of UTI or complicating urologic conditions. Included also if culture was negative because of recent antibiotic treatment (2 in each group) or contaminated with mixed flora superimposed on one pathogen having at least 100,000 CFU (4 (group 1), 2 (group 2)). EXCLUSION CRITERIA Ciprofloxacin allergy, inability to take oral medicine, severe sepsis, elevated creatinine levels, renal obstruction, pregnancy, high-risk condition (e.g. agranulocytosis).
Interventions	GROUP 1 IV switch therapy. Ciprofloxacin IV 400 mg/d for 72 hours or until afebrile for 24 hours followed by ciprofloxacin PO 1,000 mg/d. GROUP 2 Oral therapy. Ciprofloxacin 400 mg/d.
Outcomes	1. Cessation of fever (days, mean, CI). 2. Combined clinical and bacteriological cure rate under therapy (after 3 to 5 days of therapy). 3. Adverse events rate.
Notes	Of 163 enrolled, 22 patients (11/group) were excluded from analysis. Of those, 19 patients did not fulfil inclusion criteria retrospectively, 2 had incomplete outcome data, 1 withdrew consent. 2 patients of each group had received other antibiotics within 24 hours before study begin and had negative urine culture at inclusion. SD calculated based on 95% CI.

Risk of bias

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

Montini 2007

Methods	Prospective multicentre RCT. Computer generated randomisation list with stratification for hospital, sex and age, block randomisation. No information whether ITT.
Participants	INCLUSION CRITERIA Number: 185 (group 1), 202 (group 2). Gender: 244 females. Age: 2 months to 6 years with normal kidney function. First UTI defined as fever, 2 consecutive positive urinalysis, 2 positive urine cultures, high blood inflammation indices. EXCLUSION CRITERIA Excluded in case of urinary tract malformation, serious illness, hypersensitivity to antibiotics.

Montini 2007 (Continued)

Interventions	GROUP 1 Oral therapy. amoxicillin/clavulanic acid 50 mg/kg/d for 10 days. GROUP 2 IV switch therapy. Ceftriaxon 50 mg/kg/d until cessation of fever followed by amoxicillin/clavulanic acid.
Outcomes	1. Cessation of fever (hours mean, SD)
Notes	Abstract only plus information from www.clinicaltrials.gov. At time of publication, 88% of required population was enrolled

Risk of bias

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

Neuhaus 2008

Methods	Prospective multicentre RCT. Computer generated randomisation list, sealed envelopes. No ITT.
Participants	INCLUSION CRITERIA Number: 78 (group 1), 72 (group 2). Gender (F/M): unknown. Age: 6 months to 16 years. Fever > 38°C, CRP > 10 mg/L, positive urine culture (catheter urine) and positive DMSA scintigraphy at beginning (signs of pyelonephritis). EXCLUSION CRITERIA Normal scintigraphy, sepsis, complex urinary abnormalities.
Interventions	GROUP 1 Oral therapy. Ceftibuten 9 mg/kg/d PO for 14 days. GROUP 2 IV switch therapy. Ceftriaxone 50 mg/kg IV for 3 days followed by ceftibuten for 11 days.
Outcomes	1. Number of patients with renal scarring (DMSA) after 6 months. 2. Adverse events rate.
Notes	Of 365 children initially enrolled and randomised, 346 had an acute DMSA scan. Children excluded because of normal DMSA scan (127). Follow-up scan and included in analysis (152).

Risk of bias

Bias	Authors' judgement	Support for judgement

Neuhaus 2008 (Continued)

Allocation concealment (selection bias)	Low risk	A - Adequate

Noorbakhsh 2004

Methods	Prospective RCT in a tertiary care centre. Randomisation list kept with principal investigator. No ITT.
Participants	INCLUSION CRITERIA Number: 24 (group 1), 30 (group 2). Gender (F/M): unknown. Age: $\leq$ 10 years. Fever, flank pain, pyuria and positive urine culture. EXCLUSION CRITERIA Severe allergy to study therapy, obstructive uropathy, renal abscess, immune-compromising disease, acute hepatic failure, clinical signs of sepsis, requirement for dialysis.
Interventions	GROUP 1 IV switch therapy. Ceftriaxone IV 50 mg/kg/d for 2 to 3 days, then cefixime 8 mg/kg/d for 8 to 12 days. GROUP 2 IV therapy. Amikacin 15 mg/kg/d or gentamicin 3 mg/kg/d with ampicillin 100 mg/kg/d for 7 to 10 days.
Outcomes	1. Combined clinical and microbiological cure rate at end of therapy.
Notes	Of 30/30 patients enrolled, only 24 (group 1) received switch therapy. The other 6 were treated IV because of lack of cefixime. These patients were not added to analysis (personal communication of author)

Risk of bias

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

Puppo 1989

Methods	Prospective RCT. Randomisation method: not stated. ITT: unclear (not stated whether 100 patients were randomised, 18 excluded afterwards, or 100 patients assessed, 18 excluded and 82 randomised).
Participants	INCLUSION CRITERIA Number: 18 (group 1), 20 (group 2). Gender (F/total): 15/22 females in total study population. Age: $>$ 18 years. Clinical symptoms of severe UTI/ pyelonephritis and positive urine culture (24/20 adults with mild UTI/ cystitis, not included in review). EXCLUSION CRITERIA

Modes of administration of antibiotics for symptomatic severe urinary tract infections (Review)

Puppo 1989 (Continued)

Hypersensitivity to drugs, pregnancy, breast feeding, severe liver or kidney disease. 78 (5% group 1, /75% group 2) had complicated pyelonephritis.

Interventions	GROUP 1 Oral therapy. Norfloxacin 400 mg twice daily for 7 days. GROUP 2 IM therapy. Aztreonam 1 g IM twice daily for 7 days.
Outcomes	1. Bacteriological cure rate at end of treatment and after 4 week interval (n, %). 2. Other outcomes not differentiated in pyelonephritis and cystitis.
Notes	Of 100 enrolled, 18 patients were excluded before or after randomisation (unclear). Only patients with pyelonephritis included in review (38), patients with cystitis (44) not included

Risk of bias

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

Regnier 1989

Methods	Prospective multicentre RCT. Randomisation table in blocks of 4, stratification according to centre. No ITT.
Participants	INCLUSION CRITERIA Number: 47 (group 1), 48 (group 2). Gender (F/total): unknown, but 4 times more females Age: > 15 years. Severe UTI defined as fever, bacteriuria, positive urine culture and pyuria or at least one clinical sign or 2 positive urine cultures. Severity defined as either fever > 39°C, age > 65 years or pre-existing nephro-urological disease or positive haemoculture. EXCLUSION CRITERIA pregnancy, breast feeding, insufficient contraception, cephalosporin allergy, renal or hepatic failure, or other chronic disease, antibiotics within 48 hours.
Interventions	GROUP 1 IV switch therapy. Ceftriaxone 2 g/d for 4 days IV followed by oral cefixime 200 mg twice daily for 11 days. GROUP 2 Parenteral therapy. IV ceftriaxone 2 g/d for 4 days followed by IM or IV ceftriaxone 1 g/d for 11 days.
Outcomes	1. Clinical cure rate at end of therapy. 2. Clinical and bacteriological cure rate at the end of treatment and after interval of 30 to 45 days. 3. Reinfection rate at end of treatment and after interval. 4. Relapse rate after interval. 5. Adverse events rate.

Regnier 1989 (Continued)

Notes	Of 97 patients enrolled, 2 patients of parenteral group were excluded from analysis because of negative urine culture at beginning. No urine culture at the end of treatment in 11/12 patients (1/12 complete loss to follow-up) and therefore exclusion from most of the outcomes. 8/6 patients lost to follow-up after 30 to 45 days.

Risk of bias

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

Sanchez 2002

Methods	Prospective RCT at a tertiary care centre. Randomisation based on computer generated numbers. No ITT.
Participants	INCLUSION CRITERIA Number: 51 (group 1), 54 (group 2). Gender (F/M): all women. Age: 18 to 75 years. Diagnosis of UTI defined as fever > 38°C, flank pain and pyuria. EXCLUSION CRITERIA Pregnancy, catheterisation, preceding antibiotic treatment, complicated UTI, sterile urine culture at beginning, hypersensitivity to cephalosporins.
Interventions	GROUP 1 Single shot IV/oral therapy. Ceftriaxone 1 g IV, then cefixime 400 mg or other oral antibiotic according to results of urine culture for 10 days. GROUP 2 IV switch therapy. Ceftriaxone 1 g/d IV until results of urine culture then oral antibiotics for a total of 10 days.
Outcomes	1. Clinical cure rate under therapy (after 3 days). 2. Clinical cure rate at end of therapy (after 10 days). 3. Bacterial cure rate under therapy (after 3 days). 4. Duration of fever (days). 5. Duration of clinical symptoms (days). 6. Adverse events rate.
Notes	Of 144 patients enrolled with clinical symptoms of UTI, 51 (group 1) and 54 (group 2) had a positive urine culture (others were excluded after randomisation).

Risk of bias

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

Vilaichone 2001

Methods	Prospective RCT at a tertiary care centre. Randomised in blocks of 4, method not stated. ITT.
Participants	INCLUSION CRITERIA Number: 18 (group 1), 18 (group 2). Gender (F/total): 9/18 (group 1) 8/18 (group 2). Age: 1 month to 15 years. Fever, > 38°C or subnormal temperatures in small infants, pyuria and/or bacteriuria and a positive urine culture from MSU or bag and a positive 99mTc-DMSA scan proving pyelonephritis. EXCLUSION CRITERIA History of previous UTI, anatomic abnormalities, neurogenic bladder, kidney failure, allergy to cephalosporin or penicillin, systemic antibiotics within 48 hours, chronic disease.
Interventions	GROUP 1 IV switch therapy. Ceftriaxon IV 75 mg/kg/d until afebrile > 24 to 48 hours, followed by oral ceftibuten 9 mg/kg/d for 10 days. GROUP 2 IV therapy. Ceftriaxone IV 75 mg/kg/d for 10 days.
Outcomes	1. Bacteriological cure rate at end of therapy (day 14). 2. Clinical cure rate after interval of 6 months. 3. Bacteriological cure rate after interval of 6 months. 4. Reinfection rate after 6 months (n, %). 5. DMSA renal scan after 0.5 year.
Notes	Of 100 patients, 64 were excluded before randomisation because of recurrent UTI (9), anatomical abnormalities (5), chronic disease (2), failure to notify (4), normal DMSA scan at beginning (18), negative urine culture (26). Hospitalisation rate cannot be compared because only mean (no SD) is given. Adverse events rate only given for IV switch group.

Risk of bias

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

UTI - urinary tract infection

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abraham 1982	Not an RCT (retrospective cohort study).
Ahmetagic 2003	RCT. Includes patients with sepsis from age 0 to 96 years. No separate data for patients with UTI. No clear inclusion criteria.
Angel 1990	RCT.

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Study	Reason for exclusion
	Unclear data presentation of 102 patients screened, 90 (45/45) were randomised into group 1 (IV switch therapy) or group 2 (oral therapy). Three patients of group 1 and 10 patients of group 2 were excluded afterwards because of positive blood culture and subsequent IV therapy. Patients with a negative urine culture (5/90). Only 39 in group 1 and 33 in group 2 had a urine culture at the end of therapy.
Benador 2001	RCT. Compares 2 switch therapies with different duration of IV antibiotics (3 days IV then 12 days PO versus 10 days IV then 5 days PO).
Buchi 1988	Not an RCT.
Bunnag 2003	Not an RCT.
Cherubin 1986	RCT. Includes patients with complicated UTI and resistant organisms. Mild UTI (cystitis), only 28% of patients had fever at inclusion, only 28% are classified as having pyelonephritis.
Concia 2006	RCT. No inclusion criteria, unclear data presentation. Compares switch therapy with IV therapy, but only 19/23 patients received switch therapy, 4 patients of switch therapy group received IV therapy only.
Cox 1987	RCT. Includes only patients with nosocomially acquired UTI. Only 17% had E. coli infection, but in 31% Pseudomonas could be isolated. Also, most patients had a Foley catheter in place when becoming infected.
Cox 1989	RCT. Includes only patients with complicated UTI.
Daly 1989	Not an RCT.
Esposito 1991	RCT. Includes patients with mild to moderate UTI not further specified, probably rather lower than upper UTI (no clear inclusion criteria, no baseline characteristics table). All included patients had liver cirrhosis.
Fang 1991	RCT. Compared oral therapy with ciprofloxacin and IV therapy with aminoglycosides in patients with complicated UTI (inclusion criteria: anatomic or functional abnormality of urinary tract).
Fass 1989	Stratified RCT. Compares ceftazidime IV versus ciprofloxacin IV/PO in 72 patients, among those 31 patients with UTI. Many of the patients in the IV group were switched to an oral beta-lactam. No randomisation within UTI strata (23 ceftazidime IV, 8 ciprofloxacin IV/PO).
Gangji 1989	RCT. Randomised 89 patients with septicaemia and among those 33 patients with UTI. No separate outcome data for UTI.
Gaut 1989	RCT. Only 5 with UTI. Patients with UTI were only included if infection was caused by P. aeruginosa or any other organism resistant to conventional antibiotics and was either complicated or severe. Typical UTI = exclusion to study.
Gelfand 1993	Not an RCT (sequential therapy group).
Giamarellou 1989	RCT.

Study	Reason for exclusion
	Patients with UTI (28/103). Comparison between ceftazidime IV or IM and pefloxacin IV or PO or sequential, but results are not documented according to mode of application.
Harding 1993	RCT. Compares oral ciprofloxacin versus standard parenteral therapy in patients with complicated UTI (inclusion criteria: complicated UTI, i.e. documented anatomical or functional abnormalities, presence of chronic catheter or recurrent episodes of UTI).
Kalager 1992	RCT. Compares sequential therapy and IV therapy in RCT including patients with systemic infections, among those 51(?) patients with UTI. Data presentation unclear and contradictory, not possible to extract data for UTI only.
Kanellakopoulou 1990	Not an RCT.
Le Conte 2001	RCT. Compares ciprofloxacin plus placebo vs ciprofloxacin plus tobramycin single shot. Ciprofloxacin was given IV in 15% and orally in 85% (in both arms).
Levtchenko 2001a	RCT. Compares 2 switch therapies with different duration of IV antibiotics (3 days IV then 15 d PO versus 7 days IV then 14 days PO).
Lorian 1994	Not an RCT (retrospective cohort study).
Matilla 1982	RCT. Compares two different sequential therapies: cephalexin versus cephradine, both initially as parenteral treatment and then as oral treatment.
Michaelis 1993	RCT. Compares two different sequential therapies: lomefloxacin versus ciprofloxacin, both initially as parenteral treatment and then as oral treatment.
Nicolle 1991	RCT. Compares oral or IV ofloxacin versus standard care in pneumonia, UTI and skin infection. Five patients with UTI, all randomised to ofloxacin, none randomised to standard care.
Paladino 1991	RCT. Compares IV antibiotics versus IV switch therapy in serious infections. Randomisation was not infection-specific, most patients had previous antibiotic treatment, 11 patients with UTI were randomised to IV therapy, 8 to switch therapy. UTI was secondary infection in 3 patients, 5 patients had complicated UTI, 5 patients had bacteraemia, a primary focus and UTI as secondary focus simultaneously. Antibiotic treatment before enrolment (51/103).
Peacock 1989	RCT. Compares sequential ciprofloxacin (IV and oral) with ceftazidime (followed by oral antibiotic) in severe infections. Number receiving oral antibiotics: 63% in ciprofloxacin group and 55% in ceftazidime group. No separation of results according to application modes.
Raz 1988	RCT. Compares IV switch therapy and IV therapy in patients with complicated UTI (inclusion criteria: complicated UTI without further definition). Enrolled were patients with prostatic obstruction, cancer, kidney stones.
Robson 1993	Not an RCT (pharmacokinetic study).
Safrin 1988	Not an RCT (retrospective cohort study).

Study	Reason for exclusion
Sannier 2000	Not an RCT (retrospective study).
Timmerman 1992	RCT. Compares IV switch therapy and IV therapy in patients with complicated UTI defined as anatomical or functional abnormality of the urinary tract, urinary tract instrumentation and/or a serious illness.

DATA AND ANALYSES

Comparison 1. Switch versus parenteral therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fever after 48 hours	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Bacteriological cure under therapy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Clinical cure at end of treatment	2	137	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.94, 1.10]
4 Bacteriological cure at end of treatment	2	76	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.92, 1.13]
5 Clinical and bacteriological cure at end of treatment	4	294	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.94, 1.04]
6 Reinfection at end of treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Clinical and bacteriological cure after interval	3	219	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.89, 1.11]
7.1 Paediatric studies	2	138	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.96, 1.10]
7.2 Adult studies	1	81	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.73, 1.16]
8 Relapse after interval	3	203	Risk Ratio (M-H, Random, 95% CI)	2.79 [0.30, 25.67]
9 Reinfection after interval	4	239	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.30, 1.90]
10 Renal scarring (DMSA scan) after 6 months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 Adverse events	4	292	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.19, 3.83]
11.1 Pediatric studies	3	195	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.30, 1.53]
11.2 Adult studies	1	97	Risk Ratio (M-H, Random, 95% CI)	12.24 [0.71, 211.37]

Analysis 1.1. Comparison 1 Switch versus parenteral therapy, Outcome 1 Fever after 48 hours.

Study or subgroup	Parenteral therapy n/N	Switch therapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Fischbach 1989	2/10	0/10		5[0.27,92.62]

Analysis 1.2. Comparison 1 Switch versus parenteral therapy, Outcome 2 Bacteriological cure under therapy.

Study or subgroup	Switch therapy n/N	Parenteral therapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Fischbach 1989	7/9	10/10		0.79[0.54,1.15]

Analysis 1.3. Comparison 1 Switch versus parenteral therapy, Outcome 3 Clinical cure at end of treatment.

Study or subgroup	Switch therapy n/N	Parenteral therapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Childs 1990	19/19	20/21		37.18%	1.05[0.92,1.2]
Regnier 1989	44/47	47/50		62.82%	1[0.9,1.1]
Total (95% CI)	66	71		100%	1.01[0.94,1.1]
Total events: 63 (Switch therapy), 67 (Parenteral therapy)					
Heterogeneity: Tau ² =0; Chi ² =0.34, df=1(P=0.56); I ² =0%					
Test for overall effect: Z=0.34(P=0.73)					

Analysis 1.4. Comparison 1 Switch versus parenteral therapy, Outcome 4 Bacteriological cure at end of treatment.

Study or subgroup	Switch therapy n/N	Parenteral therapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Childs 1990	18/19	18/21		23.23%	1.11[0.9,1.36]
Vilaichone 2001	18/18	18/18		76.77%	1[0.9,1.11]
Total (95% CI)	37	39		100%	1.02[0.92,1.13]
Total events: 36 (Switch therapy), 36 (Parenteral therapy)					
Heterogeneity: Tau ² =0; Chi ² =1.09, df=1(P=0.3); I ² =8.46%					
Test for overall effect: Z=0.45(P=0.65)					

Analysis 1.5. Comparison 1 Switch versus parenteral therapy, Outcome 5 Clinical and bacteriological cure at end of treatment.

Analysis 1.6. Comparison 1 Switch versus parenteral therapy, Outcome 6 Reinfection at end of treatment.

Analysis 1.7. Comparison 1 Switch versus parenteral therapy, Outcome 7 Clinical and bacteriological cure after interval.

Analysis 1.8. Comparison 1 Switch versus parenteral therapy, Outcome 8 Relapse after interval.

Analysis 1.9. Comparison 1 Switch versus parenteral therapy, Outcome 9 Reinfection after interval.

Analysis 1.10. Comparison 1 Switch versus parenteral therapy, Outcome 10 Renal scarring (DMSA scan) after 6 months.

Analysis 1.11. Comparison 1 Switch versus parenteral therapy, Outcome 11 Adverse events.

Comparison 2. Oral versus switch therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical and bacteriological cure under therapy	3	599	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.98, 1.02]
2 Clinical and bacteriological cure at end of treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Reinfection at end of treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Relapse at end of treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Clinical and bacteriological cure rate after interval	3	493	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.93, 1.01]
6 Reinfection after interval	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Symptomatic superinfection	1	287	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.27, 1.67]
6.2 Symptomatic and asymptomatic superinfection	2	341	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.29, 1.42]
7 Relapse after interval	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Renal scarring (DMSA scan) after 6 months	2	424	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.35, 2.16]
9 Mean time to cessation of fever (hours)	3	834	Mean Difference (IV, Random, 95% CI)	0.40 [-2.94, 3.74]
10 Adverse events	2	506	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.06, 15.02]

Analysis 2.1. Comparison 2 Oral versus switch therapy, Outcome 1 Clinical and bacteriological cure under therapy.

Analysis 2.2. Comparison 2 Oral versus switch therapy, Outcome 2 Clinical and bacteriological cure at end of treatment.

Analysis 2.3. Comparison 2 Oral versus switch therapy, Outcome 3 Reinfection at end of treatment.

Analysis 2.4. Comparison 2 Oral versus switch therapy, Outcome 4 Relapse at end of treatment.

Analysis 2.5. Comparison 2 Oral versus switch therapy, Outcome 5 Clinical and bacteriological cure rate after interval.

Analysis 2.6. Comparison 2 Oral versus switch therapy, Outcome 6 Reinfection after interval.

Analysis 2.7. Comparison 2 Oral versus switch therapy, Outcome 7 Relapse after interval.

Analysis 2.8. Comparison 2 Oral versus switch therapy, Outcome 8 Renal scarring (DMSA scan) after 6 months.

Analysis 2.9. Comparison 2 Oral versus switch therapy, Outcome 9 Mean time to cessation of fever (hours).

Analysis 2.10. Comparison 2 Oral versus switch therapy, Outcome 10 Adverse events.

Comparison 3. Oral versus parenteral therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bacteriological cure at end of treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Bacteriological cure after interval	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Oral versus parenteral therapy, Outcome 1 Bacteriological cure at end of treatment.

Study or subgroup	Parenteral therapy n/N	Oral therapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Puppo 1989	20/20	13/18		1.37[1.02,1.84]

Analysis 3.2. Comparison 3 Oral versus parenteral therapy, Outcome 2 Bacteriological cure after interval.

Study or subgroup	Parenteral therapy n/N	Oral therapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Puppo 1989	20/20	9/18		1.95[1.24,3.08]

Comparison 4. Single shot/oral versus switch therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure under therapy	2	225	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.86, 1.02]
2 Bacterial cure under therapy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Mean time to cessation of fever (days)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Mean time of clinical symptoms (days)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Clinical cure at end of therapy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Bacterial cure at end of therapy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Adverse events	2	225	Risk Ratio (M-H, Random, 95% CI)	4.00 [0.46, 34.75]

Analysis 4.1. Comparison 4 Single shot/oral versus switch therapy, Outcome 1 Clinical cure under therapy.

Analysis 4.2. Comparison 4 Single shot/oral versus switch therapy, Outcome 2 Bacterial cure under therapy.

Analysis 4.3. Comparison 4 Single shot/oral versus switch therapy, Outcome 3 Mean time to cessation of fever (days).

Analysis 4.4. Comparison 4 Single shot/oral versus switch therapy, Outcome 4 Mean time of clinical symptoms (days).

Analysis 4.5. Comparison 4 Single shot/oral versus switch therapy, Outcome 5 Clinical cure at end of therapy.

Study or subgroup	Switch therapy n/N	Single shot therapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Sanchez 2002	54/54	51/51		1[0.96,1.04]
Favours single shot 0.1 0.2 0.5 1 2 5 10 Favours switch				

Analysis 4.6. Comparison 4 Single shot/oral versus switch therapy, Outcome 6 Bacterial cure at end of therapy.

Study or subgroup	Switch therapy n/N	Single shot therapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Millar 1995	41/53	46/57		0.96[0.79,1.16]
Favours single shot 0.5 0.7 1 1.5 2 Favours switch				

Analysis 4.7. Comparison 4 Single shot/oral versus switch therapy, Outcome 7 Adverse events.

Study or subgroup	Single shot therapy n/N	Switch therapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Millar 1995	4/60	1/60		100%	4[0.46,34.75]
Sanchez 2002	0/51	0/54			Not estimable
Total (95% CI)	111	114		100%	4[0.46,34.75]
Total events: 4 (Single shot therapy), 1 (Switch therapy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.26(P=0.21)					
Favours single shot 0.01 0.1 1 10 100 Favours switch					

Comparison 5. Single shot/oral versus oral therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical and bacteriological cure under therapy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Bacteriological cure under therapy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Reinfection or relapse after interval	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 Single shot/oral versus oral therapy, Outcome 1 Clinical and bacteriological cure under therapy.

Study or subgroup	Oral therapy n/N	Single shot therapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Baker 2001	30/35	30/34		0.97[0.81,1.14]
Favours single shot 0.5 0.7 1 1.5 2 Favours oral				

Analysis 5.2. Comparison 5 Single shot/oral versus oral therapy, Outcome 2 Bacteriological cure under therapy.

Study or subgroup	Oral therapy n/N	Single shot therapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Baker 2001	31/35	31/34		0.97[0.83,1.14]
Favours single shot 0.5 0.7 1 1.5 2 Favours oral				

Analysis 5.3. Comparison 5 Single shot/oral versus oral therapy, Outcome 3 Reinfection or relapse after interval.

Study or subgroup	Single shot therapy n/N	Oral therapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Baker 2001	0/34	0/35		Not estimable
Favours single shot 0.1 0.2 0.5 1 2 5 10 Favours oral				

Analysis 5.4. Comparison 5 Single shot/oral versus oral therapy, Outcome 4 Adverse events.

Study or subgroup	Single shot therapy n/N	Oral therapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Baker 2001	4/34	3/35		1.37[0.33,5.68]
Favours single shot 0.1 0.2 0.5 1 2 5 10 Favours oral				

ADDITIONAL TABLES

Table 1. Methodological quality of included studies

Study ID	Concealed allocation	Blinding patients	Blinding clinicians	Blinding outcomes	Intention-to-treat	Enrolled/evaluated	Dropouts
Baker 2001	Adequate	No	Yes	Yes	No	87/69	4/73 (5%)
Childs 1990	Adequate	No	No	Not stated	No	63/40	7/63 (11%)
Fischbach 1989	Unclear	No	No	Not stated	Not stated	?/20	0%
Francois 1997	Adequate	No	No	Not stated (blinded in case of ambiguity and resolution by third party)	No	147/128	Group 1: 7 (11%) Group 2: 12 (18%)
Gok 2001	Unclear	No	No	Not stated	Not stated	?/54	Unclear
Hoberman 1999	Adequate	No	No	Yes	Yes	306/306-272 (depending on outcome)	Group 1: 21 (14%) Group 2: 13 (8%)
Millar 1995	Adequate	No	No	Yes	Yes	120/110	Group 1: 3 (5%) Group 2: 7 (12%)
Mombelli 1999	Adequate	No	No	Yes	No	163/141	2/141 (1%)
Montini 2007	Adequate	No	No	Not stated	Not stated	387(=88% sample size)/387	0%
Neuhaus 2008	Adequate	No	No	Yes	No	365/152	86/365 (24%)
Noorbakhsh 2004	Unclear	No	No	Yes	No	60/54	0%
Puppo 1989	Unclear	No	No	Not stated	No (Unclear)	100/82 (number included in this review: 38)	0%
Regnier 1989	Unclear	No	No	Not stated	No	97/95 (81 after interval)	Group 1: 6 (12.5%) Group 2: 8 (17%)

Table 1. Methodological quality of included studies *(Continued)*

Sanchez 2002	Unclear	No	No	Not stated	No	144/105	0%
Vilaichone 2001	Unclear	No	No	Not stated	Yes	36/36	0%

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	#1 MeSH descriptor Urinary Tract Infections explode all trees #2 MeSH descriptor Bacteriuria explode all trees #3 MeSH descriptor Pyuria explode all trees #4 MeSH descriptor Pyelonephritis explode all trees #5 MeSH descriptor Cystitis explode all trees #6 MeSH descriptor Urethritis explode all trees #7 uti in Clinical Trials #8 pyelonephritis in Clinical Trials #9 bacteriuria or pyuria in Clinical Trials #10 (urin* or kidney* or renal) and (infect* or inflam*) in Clinical Trials #11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) #12 MeSH descriptor Anti-Bacterial Agents explode all trees #13 MeSH descriptor Anti-Infective Agents, Urinary explode all trees #14 antibiotic* in Clinical Trials #15 (#12 OR #13 OR #14) #16 MeSH descriptor Administration, Oral explode all trees #17 oral* or (per next os) or po in Clinical Trials #18 MeSH descriptor Injections explode all trees #19 MeSH descriptor Infusions, Parenteral explode all trees #20 MeSH descriptor Infusions, Intravenous explode all trees #21 intra-venous* or intravenous* or iv or parenteral* or intramuscular* or intra-muscular* or im or (intra next muscular*) in Clinical Trials #22 (#16 OR #17 OR #18 OR #19 OR #20 OR #21) #23 (#11 AND #15 AND #22)
MEDLINE	1. urinary tract infections/ or bacteriuria/ or pyuria/ or pyelonephritis/ 2. ((urin\$ or kidney\$ or renal) and (infect\$ or inflam\$)).tw. 3. exp Cystitis/ 4. exp Urethritis/ 5. uti.tw. 6. pyelonephritis.tw. 7. (bacteriuria or pyuria).tw. 8. or/1-7 9. exp Anti-Bacterial Agents/ 10. exp Anti-Infective Agents, Urinary/ 11. antibiotic\$.tw. 12. or/9-11 13. exp Injections/ 14. exp Infusions Parenteral/ 15. (intra-venous\$ or intravenous\$ or iv or parenteral\$).tw. 16. or/13-15 17. exp Administration Oral/ 18. (oral\$ or per os or po).tw. 19. or/17-18 20. or/16,19 21. and/16,19 22. and/8,12,20 23. and/8,12,21
EMBASE	1. urinary tract infections/ or bacteriuria/ or pyuria/ or pyelonephritis/ 2. ((urin\$ or kidney\$ or renal) and (infect\$ or inflam\$)).tw. 3. exp Cystitis/

(Continued)

4. exp Urethritis/
5. uti.tw.
6. pyelonephritis.tw.
7. (bacteriuria or pyuria).tw.
8. or/1-7
9. exp Anti-Bacterial Agents/
10. exp Anti-Infective Agents, Urinary/
11. antibiotic\$.tw.
12. or/9-11
13. exp Injections/
14. exp Infusions Parenteral/
15. (intra-venous\$ or intravenous\$ or iv or parenteral\$).tw.
16. or/13-15
17. exp Administration Oral/
18. (oral\$ or per os or po).tw.
19. or/17-18
20. or/16,19
21. and/16,19
22. and/8,12,20
23. and/8,12,21

WHAT'S NEW

Date	Event	Description
22 July 2014	Amended	Minor copy edit of 2 study names
11 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

AP - protocol development, literature search, data abstraction, data entry, data analysis, writing of review

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Anti-Bacterial Agents [*administration & dosage]; Anti-Infective Agents, Urinary [*administration & dosage]; Randomized Controlled Trials as Topic; Urinary Tract Infections [*drug therapy]

MeSH check words

Humans