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Antibiotics for treating lower urinary tract infection in children (Review)

Fitzgerald A, Mori R, Lakhanpaul M, Tullus K

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[Intervention Review]

Antibiotics for treating lower urinary tract infection in children

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ABSTRACT

Background

Urinary tract infection (UTI) is one of the most common bacterial infections in infants and children. Lower UTI is the most commonly presenting and in the majority of cases can be easily treated with a course of antibiotic therapy with no further complications. A number of antimicrobials have been used to treat children with lower UTIs; however is it unclear what are the specific benefits and harms of such treatments.

Objectives

This review aims to summarise the benefits and harms of antibiotics for treating lower UTI in children.

Search methods

We searched the Renal Group's Specialised Register (April 2012), CENTRAL (*The Cochrane Library* 2012, Issue 5), MEDLINE OVID SP (from 1966), and EMBASE OVID SP (from 1988) without language restriction.
Date of last search: May 2012.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs in which antibiotic therapy was used to treat bacteriologically proven, symptomatic, lower UTI in children aged zero to 18 years in primary and community healthcare settings were included.

Data collection and analysis

Two authors independently assessed study quality and extracted data. Statistical analyses were performed using the random effects model and the results expressed as risk ratios (RR) with 95% confidence intervals (CI).

Main results

Sixteen RCTs, analysing 1,116 children were included. Conventional 10-day antibiotic treatment significantly increased the number of children free of persistent bacteriuria compared to single-dose therapy (6 studies, 228 children: RR 2.01, 95%CI 1.06 to 3.80). No heterogeneity was observed. Persistent bacteriuria at the end of treatment was reported in 24% of children receiving single-dose therapy compared to 10% of children who were randomised to 10-day therapy. There were no significant differences between groups for persistent symptoms, recurrence following treatment, or re-infection following treatment. There was insufficient data to analyse the effect of antibiotics on renal parenchymal damage, compliance, development of resistant organisms or adverse events. Despite the inclusion of 16 RCTs, methodological weakness and small sample sizes made it difficult to conclude if any of the included antibiotics or regimens were superior to another.

Authors' conclusions

Although antibiotic treatment is effective for children with UTI, there are insufficient data to answer the question of which type of antibiotic or which duration is most effective to treat symptomatic lower UTI. This review found that 10-day antibiotic treatment is more likely to eliminate bacteria from the urine than single-dose treatments. No differences were observed for persistent bacteriuria, recurrence or re-infection between short and long-course antibiotics where the antibiotic differed between groups. This data adds to an existing Cochrane review comparing short and long-course treatment of the same antibiotic who also reported no evidence of difference between short and long-course antibiotics.

PLAIN LANGUAGE SUMMARY

Antibiotics for lower urinary tract infection in children

Urinary tract infection (UTI) is one of the most common bacterial infections in infants and children. The most commonly presenting infection of the urinary tract is known as cystitis and in the majority of cases can be easily treated with a course of antibiotic therapy with no further complications. This review identified 16 studies investigating antibiotics for UTI in children. Results suggest that 10-day antibiotic treatment is more likely to eliminate bacteria from the urine than single-dose treatments; there was not enough data to draw conclusions about other treatment durations, or effectiveness of particular antibiotics. Although antibiotic treatment is effective for children with UTI, there are insufficient data to recommend any specific regimen.

Summary of findings for the main comparison. Single-dose versus short-course (3-7 days) antibiotics for treating lower urinary tract infection in children

Single-dose versus short-course (3-7 days) antibiotics for treating lower urinary tract infection in children

Patient or population: children with lower urinary tract infection
Settings: outpatient or emergency departments
Intervention: single-dose
Comparison: short-course (3-7 days)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Short-course (3-7 days)	Single-dose				
Persistent bacteriuria Follow-up: 1-7 days	**Study population**		**RR 1.3** (0.65 to 2.62)	145 (2 studies)	⊕⊝⊝⊝ **very low** [1,2]	
	200 per 1000	**260 per 1000** (130 to 524)				
	Medium risk population					
	245 per 1000	**318 per 1000** (159 to 642)				
Recurrence	**Study population**		**RR 1.5** (0.43 to 5.26)	145 (2 studies)	⊕⊝⊝⊝ **very low** [1,2]	
	100 per 1000	**150 per 1000** (43 to 526)				
	Medium risk population					
	85 per 1000	**128 per 1000** (37 to 447)				
Re-infection	**Study population**		**RR 0.16** (0.02 to 1.26)	45 (1 study)	⊕⊝⊝⊝ **very low** [3,4]	
	250 per 1000	**40 per 1000** (5 to 315)				

Medium risk population		
250 per 1000	**40 per 1000** (5 to 315)	

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

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

[1] Neither study reported allocation concealment or blinding; one reported adequate randomisation method, but the other did not; ITT was used in both studies, but one had losses to follow-up > 10%.
[2] Small number of participants (≤ 50/group) and wide CI that crosses 1
[3] Allocation concealment and blinding not reported. Random numbers table and ITT analyses used and no losses to follow-up.
[4] Very small numbers of patients (45)

Summary of findings 2. Single-dose versus conventional 10-day antibiotic treatment for treating lower urinary tract infection in children

Single-dose versus conventional 10-day antibiotic treatment for treating lower urinary tract infection in children

Patient or population: children with lower urinary tract infection
Settings: outpatient and/or emergency department
Intervention: single-dose
Comparison: conventional 10-day treatment

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Conventional 10-day treatment	**Single-dose**				
Persistent bacteriuria	**Study population**		**RR 2.01** (1.06 to 3.8)	228 (6 studies)	⊕⊝⊝⊝ **very low** [1,2]	
	104 per 1000	**209 per 1000** (110 to 395)				

	Medium risk population				
	126 per 1000	**253 per 1000** (134 to 479)			
Persistent symptoms	**Study population**		**RR 0.29** (0.03 to 2.5)	30 (1 study)	⊕⊝⊝⊝ **very low** [3,4]
	214 per 1000	**62 per 1000** (6 to 535)			
	Medium risk population				
	214 per 1000	**62 per 1000** (6 to 535)			
Persistent bacteriuria and symptoms	**Study population**		**RR 1.83** (0.18 to 18.84)	46 (1 study)	⊕⊝⊝⊝ **very low** [5,6]
	45 per 1000	**82 per 1000** (8 to 848)			
	Medium risk population				
	46 per 1000	**84 per 1000** (8 to 867)			
Recurrence	**Study population**		**RR 1.38** (0.55 to 3.5)	79 (2 studies)	⊕⊝⊝⊝ **very low** [7,8]
	158 per 1000	**218 per 1000** (87 to 553)			
	Medium risk population				
	154 per 1000	**213 per 1000** (85 to 539)			

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

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

[1] Only 1/6 studies reported randomisation method; no study reported allocation concealment; 1/6 studies reported blinding; 1/6 studies reported ITT analyses.
[2] Number of patients < 250 across all groups
[3] Randomisation method, allocation concealment, and blinding not reported, ITT analysis not used.
[4] Very small numbers of patients (31)
[5] Randomisation method and allocation concealment not reported. Open label study. ITT analysis not used and losses to follow-up > 10%
[6] Very small numbers of patients (59)
[7] Neither study reported allocation concealment. One reported using a random numbers table, the other reported blinding. Neither study used ITT analysis.
[8] Number of participants is small, < 25 in each group across both studies. CI are wide and include 1.

Summary of findings 3. Short (3-7 days) long-course (10-14 days) antibiotics for treating lower urinary tract infection in children

Short (3-7 days) versus long-course (10-14 days) antibiotics for treating lower urinary tract infection in children

Patient or population: children with lower urinary tract infection
Settings: paediatric department (1); not stated (3)
Intervention: short-course (3-7 days)
Comparison: long-course (10-14 days)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Long-course (10-14 days)	Short-course (3-7 days)				
Persistent bacteriuria	**Study population**		**RR 1.1** (0.68 to 1.77)	265 (3 studies)	⊕⊖⊖⊖ **very low** [1,2]	
	186 per 1000	**205 per 1000** (126 to 329)				
	Medium risk population					
	185 per 1000	**204 per 1000** (126 to 327)				
Recurrence	**Study population**		**RR 1.14** (0.7 to 1.86)	363 (4 studies)	⊕⊖⊖⊖ **very low** [3,4]	
	127 per 1000	**145 per 1000** (89 to 236)				
	Medium risk population					
	100 per 1000	**114 per 1000** (70 to 186)				

Re-infection	**Study population**		**RR 0.88** (0.44 to 1.74)	211 (2 studies)	⊕⊖⊖⊖ **very low** [4,5]
	147 per 1000	**129 per 1000** (65 to 256)			
	Medium risk population				
	154 per 1000	**136 per 1000** (68 to 268)			

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

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

[1] No study reported blinding. One study was quasi-RCT using alternation; the other two studies did not report randomisation method. One study reported allocation concealment and two studies reported ITT analyses.
[2] Number of patients across groups was reasonably small (265) and CIs are wide and cross 1
[3] No explanation was provided
[4] CI crosses 1
[5] Randomisation method and blinding were not reported in either study. Allocation concealment and ITT analysis was adequate in one of the two studies.

Summary of findings 4. 10-day trimethoprim versus 10-day trimethoprim+sulfamethoxazole for treating lower urinary tract infection in children

10-day trimethoprim versus 10-day trimethoprim+sulfamethoxazole for treating lower urinary tract infection in children

Patient or population: children with lower urinary tract infection
Settings: outpatients department
Intervention: 10-day trimethoprim
Comparison: 10-day trimethoprim+sulfamethoxazole

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	10-day trimethoprim +sulfamethoxazole	**10-day trimethoprim**				

Persistent bacteriuria	**Study population**		**RR 1.93** (0.38 to 9.76)	59 (1 study)	⊕⊖⊖⊖ **very low** [1,2]
	69 per 1000	**133 per 1000** (26 to 673)			
	Medium risk population				
	69 per 1000	**133 per 1000** (26 to 673)			
Persistent symptoms	**Study population**		**RR 4.84** (0.24 to 96.66)	59 (1 study)	⊕⊖⊖⊖ **very low** [1,2]
	0 per 1000	**0 per 1000** (0 to 0)			
	Medium risk population				
	0 per 1000	**0 per 1000** (0 to 0)			
Recurrence	**Study population**		**RR 2.9** (0.12 to 68.5)	59 (1 study)	⊕⊖⊖⊖ **very low** [1,2]
	0 per 1000	**0 per 1000** (0 to 0)			
	Medium risk population				
	0 per 1000	**0 per 1000** (0 to 0)			

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

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

[1] Randomisation method and allocation concealment were not reported. Investigator blind only. No ITT analysis and loss to follow-up > 10%
[2] Very small numbers of patients (59) and CI is very wide and crosses 1

Summary of findings 5. 10-day cefadroxil versus 10-day ampicillin for treating lower urinary tract infection in children

10-day cefadroxil versus 10-day ampicillin for treating lower urinary tract infection in children

Patient or population: children with lower urinary tract infection
Settings: not stated
Intervention: 10-day cefadroxil
Comparison: 10-day ampicillin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	10-day ampicillin	10-day cefadroxil				
Persistent bacteriuria	Study population		RR 0.33 (0.01 to 7.62)	32 (1 study)	⊕⊖⊖⊖ very low [1,2]	
	62 per 1000	21 per 1000 (1 to 480)				
	Medium risk population					
	63 per 1000	21 per 1000 (1 to 480)				
Persistent symptoms	Study population		RR 0.33 (0.01 to 7.62)	32 (1 study)	⊕⊖⊖⊖ very low [1,2]	
	62 per 1000	21 per 1000 (1 to 480)				
	Medium risk population					
	63 per 1000	21 per 1000 (1 to 480)				

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

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

Very low quality: We are very uncertain about the estimate.

[1] Randomisation method, allocation concealment and blinding not reported.
[2] Very small numbers of patients (32) and CIs are very wide and cross 1

Summary of findings 6. Single-dose fosfomycin versus single-dose netilmicin for treating lower urinary tract infection in children

Single-dose fosfomycin versus single-dose netilmicin for treating lower urinary tract infection in children

Patient or population: children with lower urinary tract infection
Settings: outpatients department
Intervention: single-dose fosfomycin
Comparison: single-dose netilmicin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Single-dose netilmicin	Single-dose fosfomycin				
Persistent bacteriuria	**Study population**		**RR 3.15** (0.68 to 14.64)	135 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	
	31 per 1000	**98 per 1000** (21 to 454)				
	Medium risk population					
	31 per 1000	**98 per 1000** (21 to 454)				
Recurrence	**Study population**		**RR 0.63** (0.26 to 1.56)	135 (1 study)	⊕⊖⊖⊖ **very low** [1,2]	
	156 per 1000	**98 per 1000** (41 to 243)				
	Medium risk population					
	156 per 1000	**98 per 1000** (41 to 243)				

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

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

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

[1] Randomisation method, allocation concealment and blinding not reported.
[2] Number of patients is reasonably small (135) and CIs are very wide and crossed 1

BACKGROUND

Urinary tract infection (UTI) is one of the most common bacterial infections in infants and children and the most common bacterial infection in infants under three months (Stanley 2005). Infection of the urinary tract presents in three ways; as covert bacteriuria on screening; non-systemic symptoms and infection limited to the urethra and bladder (cystitis or lower UTI); or systemic symptoms and infection of the kidneys (pyelonephritis or upper UTI). Lower UTI is the most commonly presenting and in the majority of cases can be easily treated with a course of antibiotic therapy with no further complications. Some children, particularly young infants who are unable to describe how they feel, present with non-specific symptoms making it difficult to diagnose as either lower or upper UTI, whereas older children present with more specific complaints such as dysuria or frequency. The prognosis of lower UTI in childhood is largely unknown. The relationship between UTI, renal scarring and vesicoureteric reflux (VUR) is unclear, as is the progression of lower UTI to pyelonephritis and subsequent damage to the kidneys. Current practice and treatment decisions are not underpinned by strong evidence and are largely the result of clinical judgment and the biological plausibility of future kidney damage.

It is difficult to obtain accurate estimates of the number of infants and children who will present with a lower UTI during childhood. Current practice in most countries is based on historical data from studies conducted in secondary and tertiary referral centres and renal registries. This fails to adequately describe the larger primary care population for whom very limited population-based data, of robust quality, exists. Of the population-based studies available, variable incidence rates, ranging from approximately 0.1% (Messi 1988) to 3% (Winberg 1974) have been presented. The cumulative incidence of childhood UTI is likely to be somewhere between 5% and 12% (Coulthard 1997; Hellstrom 1991).

A number of antimicrobials have been used to treat children with lower UTIs; however there is neither agreement on the most effective agent, nor the optimal dosage. This review aims to evaluate the benefits and harms of antibiotics used to treat lower childhood UTI by investigating the alleviation of symptoms and persistence of bacteriuria following treatment, recurrent symptomatic UTI and renal parenchymal damage.

An existing Cochrane review investigates antibiotic therapy for acute pyelonephritis in children (Hodson 2007) and another compared short to standard duration oral antibiotic treatment for acute UTI in children (Michael 2003). The latter concluded that a 2-4 day course of oral antibiotics appears to be as effective as 7-14 days in eradicating lower tract UTI (cystitis) in children. Two additional reviews were identified (Keren 2002; Tran 2001) comparing the efficacies of single-dose, short-course and standard course antimicrobial therapy for childhood UTI. This review provides additional data in Cochrane format, particularly on the duration of antibiotic therapy.

OBJECTIVES

This review aimed to summarise the benefits and harms of antibiotics for treating bacteriologically proven, symptomatic, lower UTI in children.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in which antibiotic therapy was used to treat lower UTI in children. The first period of randomised cross-over studies was also included.

Types of participants

Inclusion criteria

- Children aged zero to 18 years with bacteriologically proven UTI (at least one culture of a known urinary pathogen (bacterial culture > 10^5 cfu/mL) in a child with first time or recurrent UTI and who had at least one localised symptom of UTI (such as dysuria or frequency) treated with antibiotics in primary and community health care settings or an outpatient department were included.
  - Studies that primarily included children with acute pyelonephritis (at least one culture of a known urinary pathogen (bacterial culture > 10^5 cfu/mL) in a child with at least one symptom or sign of systemic illness such as fever, loin pain (or flank pain) or toxicity and additional diagnostic criteria as defined by the authors) were excluded. The symptom of fever is a controversial one; for the purposes of this review, we have excluded children who present with fever in an effort to differentiate between children with lower UTI and those with pyelonephritis.
- Children found to have renal abnormalities during the study were included, however if they had known abnormalities prior to the study they were excluded. We included children with low grade (1-2) reflux.
- Studies including patients with lower UTI and either upper UTI or covert bacteriuria were included if the data for the patients with lower UTI could be extracted separately, otherwise these studies were excluded. Any urine collection method was acceptable, including urine collection pad or bag, clean-catch method, catheter, or supra-pubic aspiration.

Exclusion criteria

- Children hospitalised for a condition not related to UTI.
- Children with bacteriologically proven UTI and symptoms or signs of systemic illness (including fever, loin pain, toxicity).
- Children with covert bacteriuria (non-symptomatic).
- Children with pre-existing renal abnormalities or known underlying renal conditions (including high grade (3-4) VUR, nephrotic syndrome and neurogenic bladder).
- Children receiving prophylactic antibiotics for UTI.
- Children receiving antibiotics for any other condition.
- Immunosuppressed children.

Types of interventions

- Antibiotic therapy (standard course) versus placebo, no therapy, a different antibiotic or alternative non-antibiotic therapy.
- Single-dose (or single-day therapy) versus standard dose.

- Mode of administration (oral, intravenous or intramuscular)

Types of outcome measures

- Persistent symptoms at completion of treatment.
- Persistent, significant bacteriuria (> 10^5 cfu/mL) at completion of treatment.
- Combinations of persistent bacteriuria (> 10^5 cfu/mL) and symptoms at completion of treatment.
- Recurrent symptomatic UTI following treatment.
- Symptomatic re-infection following treatment.
- Any renal parenchymal damage on DMSA, four to six months following UTI.
- Compliance.
- Adverse events.
- Development of resistant organisms.
- Any changes to antibiotic regimen.

Search methods for identification of studies

Electronic searches

The search strategy was comprehensive and was designed to cover two reviews being undertaken by the authors, this review and "Interventions for covert bacteriuria in children" (Fitzgerald 2012). We searched the following databases to identify relevant studies. Full details of the search strategies are reported in Appendix 1.

We searched the Cochrane Renal Group's Specialised Register (May 2012) through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

The Cochrane Renal Group's Specialised Register contains studies identified from:

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

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

Searching other resources

- Reference lists of nephrology textbooks, review articles and relevant studies.
- Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies relevant to the review. The titles and abstracts were screened independently by two authors assessed to determine which studies satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by the same authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, reports were to be grouped together and the most recent or most complete dataset used. Any discrepancy between published versions was to be highlighted. Disagreements were resolved in consultation with a third author.

Assessment of risk of bias in included studies

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

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

Measures of treatment effect

For dichotomous outcomes (e.g. symptom resolution, persistent bacteriuria, recurrent infection) results were expressed as risk ratio (RR) with 95% confidence intervals (CI). No continuous scales of measurement were used in the review.

Dealing with missing data

Any further information required from the original author was requested by written correspondence and any relevant information obtained in this manner was included in the review

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom (df), with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% corresponded to low, medium and high levels of heterogeneity.

Assessment of reporting biases

If possible, funnel plots were to be used to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Data was pooled using the random-effects model.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to explore possible sources of heterogeneity (e.g. participants, interventions and study quality). Heterogeneity among participants could be related to age and renal pathology. Heterogeneity in treatments could be related to prior agent(s) used and the agent, dose and duration of therapy. Older and newer manuscripts evaluating the same antibiotic was also analysed as a subgroup. Subgroup analyses were also used to explore paediatric sub-populations (infants, toddlers, children and adolescent groups).

- Infants: under one year of age
- Toddlers: one to under three years of age
- Children: three to under 12 years of age
- Adolescents: twelve to 18 years of age

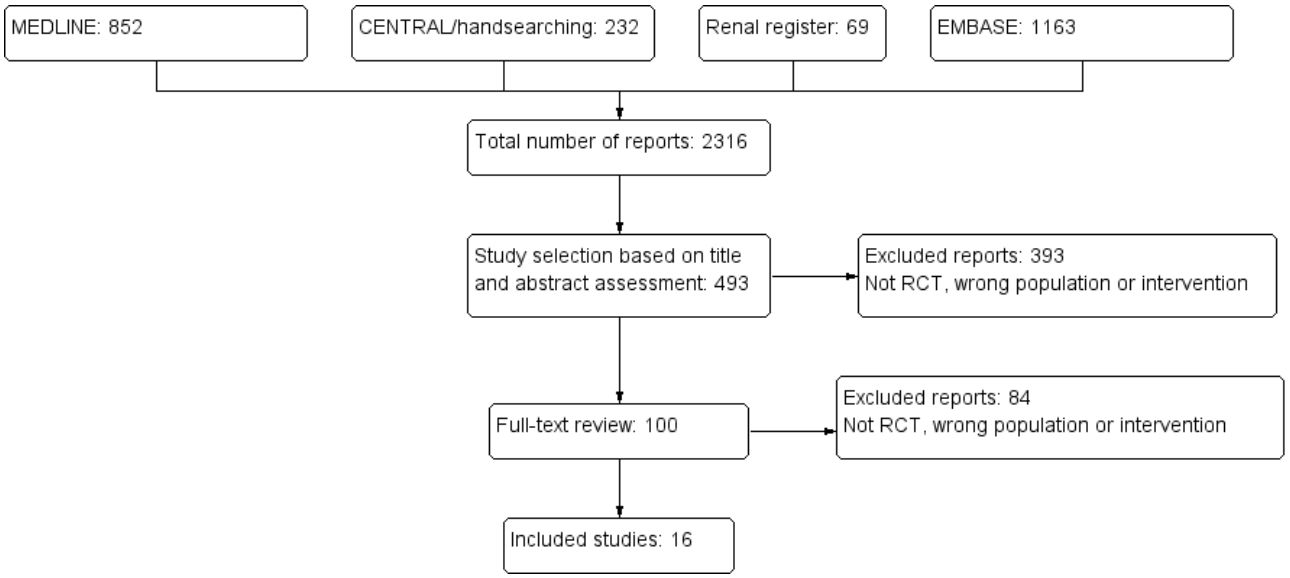
RESULTS

Description of studies

Results of the search

We initially identified 2316 potentially relevant reports of studies. After evaluating their titles and abstracts we excluded 1823 articles because they were not RCTs, included adult patients, or did not investigate antibiotics for UTI. The full-text articles of the remaining 493 studies were evaluated, with a further 393 excluded, leaving 100 potentially relevant RCTs. After further assessment 16 studies met out inclusion criteria (Figure 1).

Figure 1. Study flow diagram show study selection process



Included studies

The 16 included studies enrolled 1116 children and young people aged between two weeks and 19 years. Most were published between 1981 and 1991, with two studies published between 1999 and 2001. The median sample size was 49 patients (range: 26 to 264). All included studies used the bacteriological definition of 10^5 cfu/mL for confirming UTI and included children with non-systemic symptoms, the most common being dysuria and frequency.

Two studies compared single-dose antibiotics with short-course (3-7 days) antibiotics.

- Grimwood 1988 compared a single intramuscular gentamicin injection (3 mg/kg) with seven days of oral antibiotics sensitive to the organism cultured.
- Lidefelt 1991 compared single-dose trimethoprim (TMP) (6 mg/kg) with a five-day course of TMP (3 mg/kg, twice daily).

Six studies investigated single-dose antibiotics compared with conventional 10-day courses.

- Four studies (Avner 1983; Fine 1985; Shapiro 1981; Stahl 1984) compared single-dose amoxicillin (1-3 g) with 10-day amoxicillin (125-500 mg, thrice daily).
- Komoroski 1999 compared single intramuscular ceftriaxone (50 mg/kg) with 10-day TMP-sulfamethoxazole (TMP-SMX) (4-5 mg/kg, twice daily).
- Wallen 1983 compared single-dose intramuscular amikacin sulfate (7.5 mg/kg) with 10-day sulfisoxazole 1(50 mg/kg/d in four divided doses).

We identified four studies comparing short duration antibiotics (3-7 days) with conventional 10-day courses using different antibiotics.

- CSG 1991 compared 3-day pivmecillinam (20-40 mg/kg/d in two doses) with 10-day sulfamethizole (40-80 mg/kg/d in two doses).
- Helin 1984 compared 3-day cephalexin (25-50 mg/kg/d in two doses) with 10-day nitrofurantoin (3-4 mg/kg/d in two or three doses).
- Mitnik 1985 administered antibiotics to which the cultured organism was susceptible and treated three groups with three,

five and 10 days of antibiotics. The data for the 3-day group were included in the analyses.

- Khan 1981 administered a range of antibiotics at random including ampicillin, sulfisoxazole and cephalexin in conventional doses given orally four times a day and compared 3-day treatment with 10-day treatment.

The Cochrane review by Michael 2003 compared short (2-4 days) with long-course (7-14 days) antibiotics in children with UTI where the short and long-course antibiotic were the same, identified nine studies (CSG 1991; Gaudreault 1992; Helin 1981; Johnson 1993; Kornberg 1994; Lohr 1981; Madrigal 1988; Wientzen 1979; Zaki 1986). We have not included these comparisons, however CSG 1991 was included in both reviews as this study presented antibiotic comparisons for both the same and different antibiotics.

Two studies compared different 10-day regimens.

- Ahmed 2001 compared TMP (monotherapy) with TMP-SMX.
- Malaka-Zafirui 1984 compared cefadroxil (25 mg/kg, once daily) with ampicillin (50 mg/kg/d in four divided doses).

One study compared single-dose regimens.

- Principi 1990 compared oral fosfomycin trometamol (2 g) with intramuscular netilmicin (5 mg/kg).

In Sanchez 1990 (published only as an abstract), children were randomised to one of five antibiotics; amoxicillin, amoxicillin and clavulanic acid, cephalixin, TMP or co-trimoxazole at standard doses for seven days.

Excluded studies

We excluded 84 articles.

- Not RCT (6)
- Included children with pre-existing renal abnormalities (10)
- Included children with pyelonephritis (18)
- Included children with both pre-existing abnormalities and pyelonephritis (2)
- Included children with fever or signs of systemic illness (30)
- Included prophylactic antibiotics (5)
- Reported in a Cochrane review comparing long and short duration antibiotics (Michael 2003) (9)
- Included children without bacteriologically proven UTI (1)
- Significantly more patients were assigned to one group compared with the other suggesting non-random allocation (1)
- Four articles were excluded for other reasons (4) (see Characteristics of excluded studies)

Risk of bias in included studies

See Figure 2 and Figure 3.

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

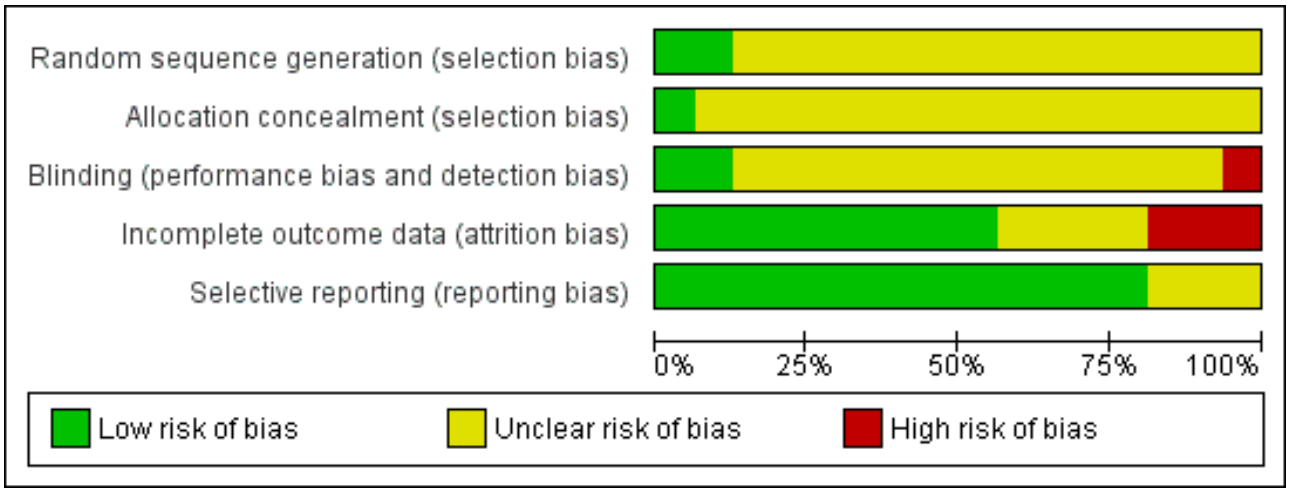
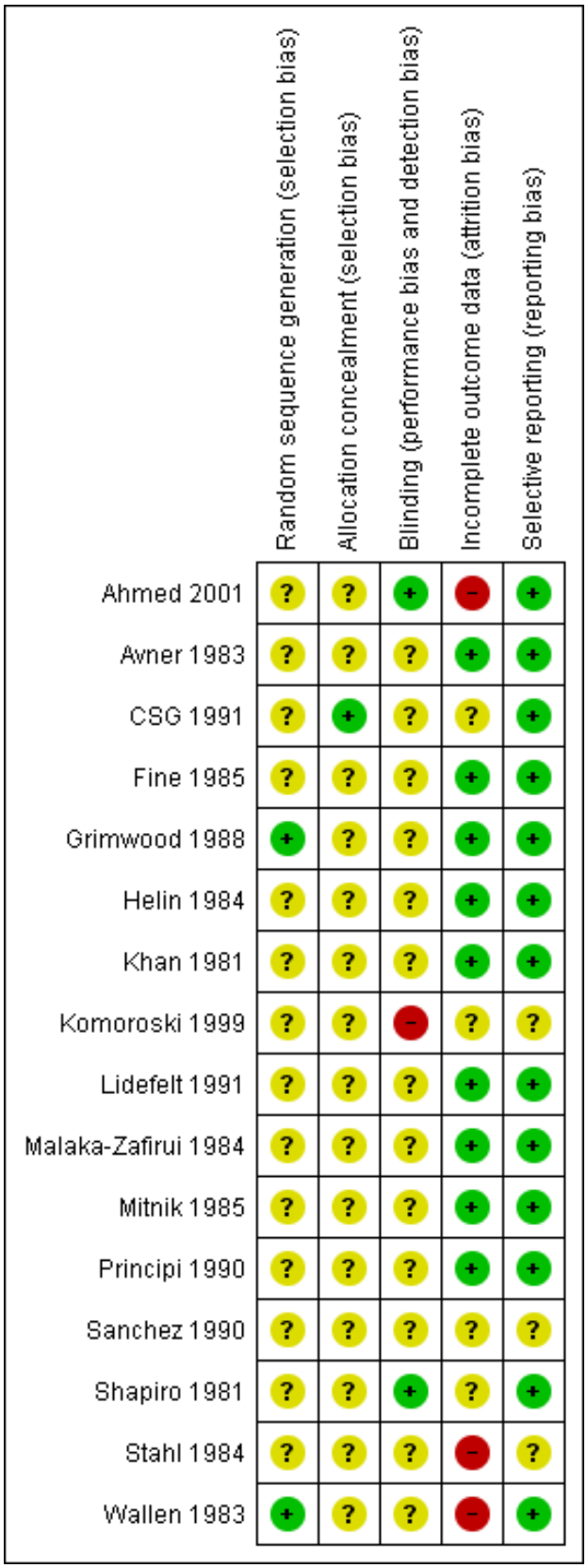


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

The quality of reporting of random sequence generation was poor. Two studies reported using random numbers tables to generate a random sequence (Grimwood 1988; Wallen 1983) and one study was quasi-randomised using alternation (Khan 1981). CSG 1991 used a block randomisation method to ensure an equal number of patients in each group. Randomisation was in blocks of six within each of the ten participating departments. No details about the way the block randomisation was performed were reported. The remaining 12 studies did not report the randomisation method.

Allocation concealment

The quality of allocation concealment was very poor. CSG 1991 reported using sealed enveloped which were prepared by the manufacturer of the study drug. The remaining 15 studies did not report allocation concealment.

Blinding

The quality of blinding was also very poor. Shapiro 1981 reported blinding both patients and physicians; Ahmed 2001 reported blinding of the investigator; and Komoroski 1999 was reported to be open label. The remaining 13 studies did not reporting blinding.

Incomplete outcome data

In two studies it appeared that children were randomised to treatment before inclusion and exclusion criteria were applied.

- CSG 1991: 26% of children randomised were lost to follow-up for a variety of reasons including not fulfilling inclusion criteria; treatment discontinued before scheduled; and did not have repeat urine cultures within the allocated time. Nineteen boys were excluded from this study because of the small number and because they were not evenly distributed between groups.
- Komoroski 1999: 37% of the children randomised were lost to follow-up. Some urine cultures showed no significant growth; some urine samples were subject to laboratory or procedural errors; and some children did not return for follow-up assessments.
- Ahmed 2001 reported that only 52% of randomised patients were analysed, no reason for attrition were given.
- Four other studies reported losses to follow-up of less than 10% (Fine 1985; Shapiro 1981; Stahl 1984; Wallen 1983).
- Sanchez 1990 was presented in an abstract and it was not clear whether patients were analysed in groups to which they were randomised.
- In the remaining eight studies, all patients were analysed in groups to which they were randomised.

Selective reporting

Most studies reported all planned outcomes. Komoroski 1999 reported relapse and recurrence, but not in a format suitable for data extraction for this review. Sanchez 1990 was published only as an abstract and it was not clear whether all planned outcomes were reported.

Effects of interventions

See: **Summary of findings for the main comparison** Single-dose versus short-course (3-7 days) antibiotics for treating lower urinary tract infection in children; **Summary of findings 2** Single-dose versus conventional 10-day antibiotic treatment for treating lower urinary tract infection in children; **Summary of findings 3** Short (3-7 days) long-course (10-14 days) antibiotics for treating lower urinary tract infection in children; **Summary of findings 4** 10-day trimethoprim versus 10-day trimethoprim+sulfamethoxazole for treating lower urinary tract infection in children; **Summary of findings 5** 10-day cefadroxil versus 10-day ampicillin for treating lower urinary tract infection in children; **Summary of findings 6** Single-dose fosfomycin versus single-dose netilmicin for treating lower urinary tract infection in children

Persistent bacteriuria at completion of treatment

Fourteen studies reported outcomes for persistent bacteriuria at completion of treatment: five studies completed follow-up urine cultures between two and five days; and one study completed follow-up urine cultures between 10 to 30 days.

Single-dose versus conventional 10-day treatment

Conventional 10-day antibiotic treatment significantly increased the number of children free of persistent bacteriuria compared to single-dose treatment (Analysis 1.1 (6 studies, 228 children): RR 2.01, 95% CI 1.06 to 3.80). No heterogeneity was observed (I^2 = 0%). The test for subgroup differences between the studies using amoxicillin in both arms and studies using other antibiotics did not show any difference (Chi^2 = 0.01, df = 1, P = 0.93, I^2 = 0%).

Single-dose versus short-course (3-7 days) treatment

There was no significant difference in persistent bacteriuria between single-dose and short-course antibiotic treatment (Analysis 2.1 (2 studies, 145 children): RR 1.30, 95% CI 0.65 to 2.62; I^2 = 30%).

Short-course (3-7 days) versus long-course (7-10 days) treatment

There was no significant difference in persistent bacteriuria between short-course and long-course antibiotic treatment in three studies (Analysis 3.1 (3 studies, 265 children): RR 1.09, 95% CI 0.67 to 1.76; I^2 = 0%).

Head-to-head studies

There were no significant differences in persistent bacteriuria between:

- TMP (10 days) versus TMP-SMX (10 days) (Analysis 4.1 (1 study, 59 children): RR 1.93, 95% CI 0.38 to 9.76);
- cefadroxil (10 days) versus ampicillin (10 days) (Analysis 5.1 (1 study, 32 children): RR 0.33, 95% CI 0.01 to 7.62); and
- fosfomycin (single-dose) versus netilmicin (single-dose) (Analysis 6.1 (1 study, 135 children): RR 3.15, 95% CI 0.26 to 1.56).

Sanchez 1990 randomised children to one of five antibiotics: amoxicillin; amoxicillin + clavulanic acid; cephalexin; TMP; or co-trimoxazole. Because of the small number of participants in each group (5 to 9) and the small number of events in each group (1 or 2) this data was unable to be included in meta-analyses. Following treatment, the number of children free of bacteriuria

in each group were 4/5 children who received amoxicillin, 2/7 children who received amoxicillin + clavulanic acid, 2/8 children who received cephalexin, 2/8 children who received TMP, and 2/9 children who received co-trimoxazole.

Persistent symptoms at completion of treatment

Three studies reported outcomes for persistent symptoms following treatment and showed no differences between treated and untreated groups; all for different antibiotic comparisons and durations.

Single-dose versus conventional 10-day treatment

There was no significant difference between single-dose treatment compared with conventional 10-day treatment (Analysis 1.2 (1 study, 30 children): RR 0.29, 95% CI 0.03 to 2.50) where 1/16 of the single-dose group had persistent symptoms compared with 3/14 of the 10-day group (Fine 1985).

TMP (10 days) versus TMP-SMX (10 days)

There was no significant difference between 10-day TMP treatment compared with 10-day TMP-SMX treatment (Analysis 4.2 (1 study, 59 children): RR 4.84, 95% CI 0.24 to 96.66) where 2/30 of the TMP group had persistent symptoms compared with 0/29 of the TMP-SMX group (Ahmed 2001).

Cefadroxil (10 days) versus ampicillin (10 days)

There was no significant difference in persistent symptoms between 10-day cefadroxil treatment compared with 10-day ampicillin treatment (Analysis 5.2 (1 study, 32 children): RR 0.33, 95% CI 0.01 to 7.62) where 0/16 of the cefadroxil group had persistent symptoms compared with 1/16 in the ampicillin group (Malaka-Zafirui 1984).

Recurrent symptomatic UTI following treatment

Ten studies reported outcomes for recurrence (with the same organism) following treatment for the initial infection; five studies reported recurrences within one month of antibiotic treatment; four studies reported recurrences between one and three months following antibiotic treatment; and one study reported recurrences at any time with a mean time of eight months.

Single-dose versus short-course (3-7 days) treatment

There was no significant difference between single-dose compared with short-course (3-7 days) treatment (Analysis 2.2 (2 studies, 145 children): RR 1.50, 95% CI 0.43 to 5.26; I^2 = 29%), where 11/75 (15%) of the single-dose had recurrence compared with 7/70 (10%) of the short-course group.

Single-dose versus conventional 10-day treatment

There was no significant difference between single-dose treatment compared to conventional 10-day treatment (Analysis 1.3 (2 studies, 79 children): RR 1.38, 95% CI 0.55 to 3.50; I^2 = 0%), where 9/41 (22%) of the single-dose group had recurrent symptomatic UTI compared with 6/38 (16%) in the 10-day group.

Short-course (3-7 days) versus long-course (7-10 days) treatment

There was no significant difference between short-course treatment compared with long-course treatment (Analysis 3.2 (4 studies, 328 children): RR 1.25, 95% CI 0.74 to 2.13; I^2 = 0%). All four studies compared 3-day to 10-day treatment. Of these four studies, 25/163 (15%) of the short-course group had recurrent symptomatic UTI compared with 21/165 (13%) of the long-course group.

Head-to-head studies

There were no significant differences in recurrent symptomatic UTI between:

- TMP (10 days) versus TMP-SMX (10 days) (Analysis 4.3 (1 study, 59 children): RR 2.90, 95% CI 0.12 to 68.50), where 1/30 in the TMP (monotherapy) group had recurrent symptomatic UTI compared with 0/29 in the TMP-SMX group; and
- fosfomycin (single-dose) versus netilmicin (single-dose) (Analysis 6.2 (1 study, 135 children): RR 0.63, 95% CI 0.26 to 1.56) where 7/71 (10%) in the single-dose fosfomycin group had recurrent symptomatic UTI compared with 10/64 (16%) in the single-dose netilmicin group.

Re-infection following treatment

Three studies reported outcomes for re-infection (with a different organism) following antibiotic treatment for the initial infection; one study reported re-infection occurring at more than one week, one study reported re-infection at 1-10 days and one study reported re-infection at any time following antibiotic treatment, with a mean time of eight months.

Single-dose versus short-course (3-7 days) treatment

There was no significant difference between single-dose compared with short-course treatment (Analysis 2.3 (1 study, 45 children): RR 0.16, 95% CI 0.02 to 1.26), where 1/25 (4%) of the single-dose group had a re-infection compared with 5/25 (20%) of the short-course group.

Short-course (3-7 days) versus long-course (7-10 days) treatment

There was no significant difference between short-course treatment compared with long-course treatment (Analysis 3.3 (2 studies, 211 children): RR 0.88, 95% CI 0.44 to 1.74; I^2 = 0%), where 14/109 (13%) of the short-course group had a re-infection compared with 15/102 (15%) of the long-course group.

Renal parenchymal damage

None of the included studies reported renal parenchymal damage. Two studies (Avner 1983, Stahl 1984) reported the use of micturating cystourethrogram or intravenous pyelogram following antibiotic therapy, however the studies were aimed to identify structural abnormalities and VUR and not renal parenchymal damage.

Compliance

Fine 1985 reported compliance with follow-up assessments. Compliance at the first scheduled follow-up appointment was 100% in the single-dose treatment group compared to 60% in the 10-day treatment group. Non-returning patients often required several phone calls and letters before returning.

Three studies reported compliance with antibiotic treatment.

- Fine 1985: 27% of the 10-day treatment group reported perfect compliance with their medication; other patients finished their medication in more than 10 days, less than 10 days, and some had not finished their medication at the time of follow-up.
- Grimwood 1988: side effects prevented two children randomised to amoxicillin from completing their course of antibiotics.
- Helin 1984: '*optimal patients compliance was assured in both groups*'.

Development of resistant organisms

While many included studies reported the antibiotic sensitivity of organisms cultured prior to treatment, most did not report development of resistant organisms during the study period. Stahl 1984, comparing single-dose with 10-day amoxicillin, reported that in each of the three single-dose patients who relapsed, the single-dose failed to clear the urinary tract of a sensitive organism, and each of the four conventional therapy patients who relapsed developed organisms resistant to amoxicillin during therapy. All of these patients subsequently responded to additional or different antibiotic therapy.

Adverse events

- Patients in five studies did not experience any side effects (Avner 1983; Helin 1984; Malaka-Zafirui 1984; Wallen 1983).
- CSG 1991: children randomised to 10-day sulfamethizole reported no side effects. Two children randomised to 3-day pivmecillinam developed urticarial rash; two children discontinued treatment due to vomiting and abdominal rash; one child had diarrhoea; and one child developed irritability and fatigue.
- Lidefelt 1991: one child randomised to single-dose TMP experienced vomiting.
- Principi 1990: two children receiving single-dose fosfomycin experienced mild and transient diarrhoea which disappeared spontaneously; one had nausea; and one had skin rash.
- Data reported in Ahmed 2001 was part of a larger study on children with both UTI and otitis media. Across both TMP and TMP-SMX groups, adverse events included vomiting, abdominal pain, diarrhoea and skin rash, although less than 5% of children experienced these symptoms.
- Fine 1985: *Candida vaginitis* occurred in three patients receiving 10-day amoxicillin.
- Komoroski 1999: two sexually active females reported vaginal itching after receiving intramuscular ceftriaxone.
- Local discomfort from injection sites was reported in two studies (Komoroski 1999; Principi 1990).
- Side effects were not reported in six studies (Grimwood 1988; Khan 1981; Mitnik 1985; Sanchez 1990; Shapiro 1981; Stahl 1984).

Subgroup analyses

We were unable to perform the pre-specified subgroup analyses. The majority of studies did not report results for different paediatric sub-populations, so this analysis could not be undertaken. Comparing older and newer manuscripts was also not possible because there were not enough 'newer' manuscripts. With the exception of Ahmed 2001 (which was the only study to compare 10-day TMP with 10-day TMP-SMX) and Komoroski 1999 (single-dose versus 10-day treatment), all studies compared were performed within a 10-year period of each other. Because the method of randomisation was not sufficiently described for most of the studies, we did not perform a sensitivity analysis that excluded quasi-RCTs. Data of randomisation, method of allocation concealment and blinding were not reported by the majority of studies and we were therefore unable to conduct sensitivity analyses comparing higher and lower quality studies.

Formal testing for publication bias using funnel plots was not possible because of the small number of studies identified.

DISCUSSION

Summary of main results

UTIs are relatively common childhood illness and require antibiotic treatment to alleviate symptoms and clear infection from the urinary tract. This review was designed to include all randomised and quasi-RCTs addressing all aspects of antibiotic treatment for children with lower UTI. Relatively few studies investigated the same comparisons, therefore meta-analyses included only a small number of studies. Nevertheless, we did not identify many instances of heterogeneity. The included studies predominantly examined bacteriological outcomes (persistent bacteriuria, recurrence, re-infection) rather than clinical outcomes (persisting symptoms) as measures of treatment efficacy. Amoxicillin or amoxicillin + clavulanic acid, cephalosporins, nitrofurantoin or TMP-SMX were the most common antibiotics given in the included studies.

Compared to single-dose therapy, 10-day antibiotic treatment was more effective in eliminating bacteriuria (RR 2.01, 95% CI 1.06 to 3.80). When we limited our analysis to only include those studies using the same antibiotic (amoxicillin) in both treatment groups, the differences no longer remained statistically significant (RR 1.97, 95% CI 0.90 to 4.33). It is unclear whether this is attributable to bias considering most of our included studies were of poor quality and sample sizes were too small to detect differences; or whether just by chance. Nevertheless, the actual numbers of children with persistent bacteriuria, 18/63 (29%) in the single-dose group compared to 8/68 (12%) of the 10-day group, represent a clinically significant difference. No differences were observed for persistent bacteriuria, recurrence or re-infection between short and long-course antibiotics where the antibiotic differed between groups; this data adds to an existing Cochrane review (Michael 2003) comparing short and long-courses of the same antibiotic who also reported no evidence of difference between short and long-course antibiotics.

No comparisons showed any significant differences between groups for persistent symptoms, recurrence, or re-infection following treatment for any other dosing regimens. In this review, there were not enough data to draw conclusions about these results; at this stage, the lack of significant differences is more likely due to the inclusion of small, poorer quality studies, rather than demonstrating equivalence between different antibiotic or dosing regimens.

Overall completeness and applicability of evidence

While there were 16 RCTs included in this review, the number of children analysed totalled 1116 (1331 randomised); only three studies included more than 100 children. The median sample

size was small (49 children), and wide CIs around most of the effect estimates suggest that studies probably lacked the statistical power to identify such differences. Of the 16 studies included, 13 were conducted between 1981 and 1990. Diagnosis of bacteriuria since this time has not changed significantly, but not all of the antibiotics used in these studies remain available. In most of the meta-analyses carried out, there were few studies included, preventing a thorough investigation of the sources of heterogeneity between study results. In particular, we could not explore the influence of specific sources of bias or methodological quality, and most importantly we could not offer results stratified by age subgroups. Adverse events were reported by some studies, but were not analysed by any included studies; this hindered our efforts to present a full picture of the benefits and harms of antibiotics treatment for lower UTI, which was our intended aim.

Quality of the evidence

The quality of the included studies for every comparison was 'very low' according to GRADE criteria (see *Summary of findings tables*). The lack of reporting of randomisation method, allocation concealment and blinding in most studies, and the large losses to follow-up in three studies are likely to contribute to biases in the results reported. Despite the inclusion of 16 studies, their methodological weakness and small sample sizes made it difficult to conclude if any of the included antibiotics or regimens were superior to another.

It was unfortunate that no study specifically addressed whether the efficacy of therapies differed according to patient age; we had planned subgroup analyses to investigate this because there are claims that UTIs can lead to long-term damage in younger children (Vernon 1997). In Fine 1985, 90% of the adolescents included were sexually active; this may have caused bias in that sexually active people (particularly women) are known to experience more frequent UTIs than those who abstain (Leibovici 1987). Four studies included young people over the age of 16 years: Shapiro 1981 included children aged 2-18 years, but the mean age was 5.6 years; Stahl 1984 included children aged 2-17 years, but the mean age was 4.75 years; Komoroski 1999 included children aged 0-18 years, but 80% were younger than 16 years; Fine 1985 included female adolescents aged 12-18 years with a mean age of 16.5 years. Although a lower tract UTI in an adolescent female is likely a very different condition than lower tract UTI in an infant or young child, post-hoc sensitivity analysis, removing Fine 1985 did not alter the conclusions for persistent bacteriuria.

None of the included studies systematically collected data on the adverse effects of antibiotics; this made our original objective of summarising the benefits and harms of antibiotic treatment difficult. Although it is not possible to compare the benefits and harms of antibiotic therapy from the included studies, from the few adverse antibiotic effects reported it seems unlikely that the expected side-effects course of antibiotics would be significant.

Data on resistant organisms were only reported in one study. There is concern regarding the increasing resistance to antibiotics, specifically to penicillins and cephalosporins. Increasing antibiotic resistance complicates the choice of empiric regimens and is likely to become an increasing problem, particularly considering the majority of health professionals prescribe antibiotics prior to knowing results of urine cultures. Utilizing local antimicrobial susceptibility data (e.g. hospital or laboratory data) to predict the antibiotics that would likely be active may be useful.

Optimal duration of antibiotic therapy in children has both cost and practical implications. Single-dose treatment, if effective can increase compliance as the treatment can be administered at the healthcare site and is likely to be cheaper. These advantages are even more important in under-resourced countries and in lower socio-economic areas.

Potential biases in the review process

The literature search included major international databases and a fairly broad search strategy was utilized to ensure all relevant studies were identified. We assume that we identified all RCTs relevant to our review question; however many of the excluded studies were foreign language articles and there is the potential that a relevant study was overlooked in the translation process. Although we stated in out protocol that we would attempt to contact investigators for missing or additional data, 10/16 studies were over 20 years old and the most recent of the remaining six studies was published a decade ago and we were not able to make contact with any investigator.

Agreements and disagreements with other studies or reviews

A Cochrane review comparing short (2-4 days) with standard (7-14 days) duration antibiotic therapy of the same antibiotic in children with UTI found no significant differences between groups and concluded that short duration of treatment offers a reasonable option for children with lower tract UTI (Michael 2003). We excluded this comparison from our analysis to avoid duplication, however we did include the comparison with different antibiotics; the results did not differ to Michael 2003; there were no differences between 2-4 day and 7-10 day antibiotic treatment. A systematic review by Keren 2002 compared short (both single-dose and 2-4 days) with long (7-10 days) treatment. Of the 17 included studies, no differences were found between groups for treatment failure or re-infection. Subgroup analyses with one day, and 2-4 day groups did not change these results. A systematic review by Tran 2001 reported that overall, short-course therapy was not as effective as conventional long-course. The review found insufficient evidence for single-dose aminoglycoside treatment to draw conclusions.

A Cochrane review in non-pregnant adult women with lower UTI found that three days of antibiotic therapy was similar to 5-10 days in achieving symptomatic cure, while the longer treatment was more effective in obtaining bacteriological cure (Milo 2005). Our review did not have enough data on persisting symptoms at the completion of treatment to investigate the differences between bacteriological and symptomatic cure.

AUTHORS' CONCLUSIONS

Implications for practice

This review adds to the evidence that short-course therapy is an appropriate therapy for children with lower UTI. While 10 days of therapy was significantly more effective than single-dose therapy, there were no differences in either this review or Michael 2003 between short and longer duration antibiotic therapy. Single-dose therapy is not recommended in children with UTI; 10-day treatment was significantly more effective in

eliminating bacteriuria. No comparisons showed any differences between groups for persisting symptoms, recurrence, or re-infection following treatment, however this is due to a paucity of RCTs rather than demonstrating equivalence. This review did not provide incontrovertible evidence about the optimal duration of antibiotic therapy or which antibiotic should be used.

Implications for research

Adequately powered RCTs investigating single-dose compared to standard (7-14 day) therapy, and single-dose compared to short duration (2-4 days) therapy should be conducted to establish the effectiveness of single-dose treatment. Additional studies comparing single-dose with 10 days of amoxicillin are needed to investigate whether single-dose increases persistent bacteriuria. Outcomes for further studies should include both clinical and bacteriological measures.

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CHARACTERISTICS OF STUDIES

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

Ahmed 2001

Methods	• Study design: parallel RCT • Study period: NS

Participants	Inclusion criteria
	• Setting/recruitment: outpatient department
	• Country: USA
	• Children aged between 6 months and 12 years with signs and symptoms of UTI, significant bacteriuria defined > 10^5 cfu/mL, and the presence of organisms susceptible to TMP and TMP-SMX. Urine collection method not reported.
	• Number: 125 randomised, 59 analysed
	  ○ Treatment group: 30
	  ○ Control group: 29
	Exclusion criteria: NS

Interventions	Treatment group • 10-day TMP (monotherapy; 10 mg/kg/d) in 2 doses Control group • 10-day TMP (8 mg/kg/d) + (SMX 40 mg/kg/d) in 2 doses
Outcomes	• Persistent bacteriuria (16-19 days following treatment) • Persistent symptoms (16-19 days following treatment) • Recurrence (16-19 days following treatment)
Notes	Source of funding: NS

Ahmed 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigators blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Less than half the randomised patients were analysed, no reason for losses to follow-up given.
Selective reporting (reporting bias)	Low risk	Planned outcomes were all analysed

Avner 1983

Methods	• Study design: parallel RCT • Study period: NS

Participants	Inclusion criteria
	• Setting/recruitment: emergency and outpatient departments, Children's Hospital Medical centre, Massachusetts General Hospital, and Cambridge Hospital, Boston
	• Country: USA
	• Children aged between 2 and 12 years with acute, lower UTIs were eligible for inclusion. Children were required to have symptoms of abdominal pain, urinary frequency, dysuria, or abnormal urinalyses consisting of hematuria with pyuria, and two midstream clean catch or one suprapubic aspiration urine culture > 10^5cfu/mL
	• Number: 49 randomised, 49 analysed
	  ◦ Treatment group: 24
	  ◦ Control group: 25
	• Sex (M/F): treatment group (2/22); control group (2/23)
	Exclusion criteria
	• Acutely ill with temperatures > 38°C, discrete flank pain, rigours, or signs of systemic toxicity; known renal disease or other systemic illness; allergic to penicillin

Interventions	Treatment group • Single-dose amoxicillin: < 23 kg (1.0 g); 23 to 32 kg (1.5 g); 32 to 45 kg (2.0 g); > 45 kg (3.0 g) Control group • Conventional 10-day amoxicillin: < 23 kg (125 mg); > 23 kg (250 mg) • Three times daily
Outcomes	• Persistent bacteriuria (4 days following treatment)

Avner 1983 *(Continued)*

Notes	• Study presents data for children with and without known abnormalities. Results for children without abnormalities are presented in this review. • Source of funding: Hoffman-Laroche Company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised were analysed
Selective reporting (reporting bias)	Low risk	Planned outcomes were all analysed

CSG 1991

Methods	• Study design: parallel RCT • Study period: NS

Participants	Inclusion criteria
	• Setting/recruitment: 10 hospital paediatric departments in and around Copenhagen
	• Country: Denmark
	• Children aged 1 to 15 years with clinical symptoms requiring immediate treatment, significant bacteriuria defined as ≥ 10^5 cfu/mL of a single bacterium in a clean catch mid-stream urine sample. Bag samples of urine were not accepted
	• Number: 359 randomised, 264 analysed; 168 included in this review
	  ○ Treatment group: 90
	  ○ Control group: 78
	• Sex (M/F): All female
	Exclusion criteria
	• Antibiotic treatment one week prior to inclusion; suspicion of allergy to penicillin or sulfonamides; required parenteral antibiotic treatment; fever > 39°C or impaired general condition; SCr > 120 µmol/L; known severe urinary tract malformations; immunosuppressive treatment or known immunodeficiency

Interventions	Treatment group • Pivmecillinam, 20-40 mg/kg/d in 2 doses for 3 days Control group • Sulfamethizole, 40-80 mg/kg/d in 2 doses for 10 days

CSG 1991 *(Continued)*

Outcomes	• Persistent bacteriuria (1-10 days following treatment)
Notes	• Children included had no previous UTI (17%), a history of UTI (31%), or recurrent UTI (52%) • Another intervention arm was included in this study, 3-day sulfamethizole. • A Cochrane review by Michael 2003 reports outcomes for this comparison which is not repeated in this review. • Source of funding: Danish Medical Research Council (5.52.11.10 and 5.52.14.86)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	To ensure an equal number of patients in each group, a block randomisation method was used. Randomisation was in blocks of 6 within each of the 10 participating departments. No details about the way the block randomisation was performed were reported.
Allocation concealment (selection bias)	Low risk	Allocation concealed by drawing consecutively numbered sealed envelopes prepared by the manufacturer
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	36 children did not fulfil inclusion criteria (26 bacteriuria not significant, 10 provided bag sample); treatment was discontinued in 6 children before scheduled; 32 children did not have urine cultures completed within 10 days from treatment; 2 children were not evaluated for other reasons; 19 boys were excluded because of the small number and because they were not evenly distributed between groups. The side effects of the 95 children who were not analysed were included as they received treatment.
Selective reporting (reporting bias)	Low risk	Planned outcomes were all analysed

Fine 1985

Methods	• Study design: parallel RCT • Study period: NS

Participants	Inclusion criteria
	• Setting/recruitment: outpatient Adolescent General Medical Clinic, University of Maryland Hospital
	• Country: USA
	• Female adolescents aged 12 to 18 years with clinical symptoms of an acute lower UTI (frequency, dysuria, hesitancy, lower abdominal pain, urgency, anorexia, low-grade fever or malaise) and significant bacteriuria defined as > 10^5 cfu/mL in a clean catch mid-stream urine sample
	• Mean age: 16.5 years
	• Number: 34 randomised, 31 analysed
	  ◦ Treatment group: 16
	  ◦ Control group: 15
	• Sex (M/F): all female
	Exclusion criteria

Fine 1985 *(Continued)*

	• Pregnancy; pyelonephritis; allergy to penicillin or concurrent antibiotic use
Interventions	Treatment group • Single-dose amoxicillin 3.0 g Control group • 10-day amoxicillin 250 mg, 3 times/day
Outcomes	• Persistent bacteriuria (2-5 days following treatment) • Persistent symptoms (2-5 days following treatment)
Notes	• 28/31 participants were sexually active • Source of funding: Maternal and Child Health Grant (MCH #000980)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants were excluded from analyses because of early pregnancy; one participant did not turn up to the follow-up appointments.
Selective reporting (reporting bias)	Low risk	Planned outcomes were all analysed

Grimwood 1988

Methods	• Study design: parallel RCT • Study period: NS
Participants	Inclusion criteria • Setting/recruitment: outpatients department, Christchurch Hospital • Country: New Zealand • Children aged 2 weeks to 12 years with significant bacteriuria defined as > 10^5 cfu/mL in 2 consecutive clean catch urine samples or any growth on supra-pubic aspiration. Children with cystitis were afebrile or had fever < 38°C, no loin pain or tenderness and were without other significant systemic symptoms. • Mean age: 4.9 years • Number of participants: 45 children Exclusion criteria • Children with pyelonephritis were also included in this study and were reported separately (and excluded from this review).

Grimwood 1988 *(Continued)*

Interventions	Treatment group • Single intramuscular gentamicin injection 3 mg/kg Control group • 7-day course of appropriate antibiotic depending on culture sensitivity in standard doses (included TMP-SMX, amoxicillin, cephlosporins).
Outcomes	• Persistent bacteriuria (1 day following treatment) • Recurrence (< 1 week following treatment) • Re-infection (> 1 week following treatment)
Notes	• 23 children with 3 or more proven UTIs during the preceding 12 months were defined as having a history of recurrent UTIs. • Source of funding: National Children's Health Research Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised were analysed
Selective reporting (reporting bias)	Low risk	Planned outcomes were all analysed

Helin 1984

Methods	• Study design: parallel RCT • Study period: NS
Participants	Inclusion criteria • Setting/recruitment: NS • Country: Sweden • Children aged under 15 years with at least 2 clinical symptoms of a UTI (including frequency, dysuria, urgency and enuresis) and significant bacteriuria defined as > 10^5 cfu/mL in a clean catch mid-stream urine sample • Mean age: 7.2 years • Number: treatment group (19); control group (24) • Sex (M/F): 1/42 Exclusion criteria

Helin 1984 *(Continued)*

	• Signs or laboratory findings suggesting upper urinary tract involvement (fever > 38.5°C, flank pain, elevated ESR and leukocytosis); known sensitivity to cephalexin and nitrofurantoin; neurogenic bladder disorder; known structural malformation of the kidneys
Interventions	Treatment group • 3-day cephalexin 25-50 mg/kg/d in 2 doses • Control group • 10-day nitrofurantoin 3-4 mg/kg/d in 2 or 3 doses
Outcomes	• Persistent bacteriuria (4-7 days following treatment) • Recurrence (any time during follow-up; mean 8 months) • Re-infection (any time during follow-up; mean 8 months)
Notes	Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised were analysed
Selective reporting (reporting bias)	Low risk	Planned outcomes were all analysed

Khan 1981

Methods	• Study design: Quasi-RCT • Study period: NS
Participants	Inclusion criteria • Setting/recruitment: Jewish Hospital and Medical Centre of Brooklyn, State University of New York, Downstate Medical Centre • Country: USA • Children aged six months to 15 years with symptoms of cystitis (including frequency and dysuria without fever) and significant bacteriuria defined as > 10^5 cfu/mL in 2 consecutive clean catch urine samples. • Mean age: 5.65 years • Number: treatment group (27); control group (27) • Sex (M/F): 4/50 Exclusion criteria

Khan 1981 *(Continued)*

	• Younger than 6 months, or older than 15 years; urinary tract malformations; abnormal SCr or BUN values.
Interventions	Treatment group • 3-day treatment Control group • 10-day treatment Antimicrobial agents were 'chosen at random' for both groups and included ampicillin, sulfisoxazole and cephalexin in conventional doses given orally 4 times/day.
Outcomes	• Persistent bacteriuria (3-7 days following treatment) • Recurrence (> 2 months following treatment)
Notes	Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Alternation
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed in groups to which they were assigned
Selective reporting (reporting bias)	Low risk	Planned outcomes were analysed. Data for re-infection was presented across cystitis, pyelonephritis and asymptomatic bacteriuria and was not reported for cystitis alone.

Komoroski 1999

Methods	• Study design: parallel RCT • Study period: NS
Participants	Inclusion criteria • Setting/recruitment: outpatient and emergency department, Arkansas Children's Hospital • Country: USA • Children aged 1 to 19 years with at 1 or more clinical symptoms of cystitis (including frequency, dysuria, enuresis, haematuria, pyuria, suprapubic tenderness) and significant bacteriuria defined > 10^4 cfu/mL of a single organism from 1 catheterized bladder specimen or >10^5 cfu/mL from a nitrite-positive specimen. Urine cultures were also considered positive if > 10^5 cfu/mL of a single organism was obtained from a single clean-catch specimen, and the second specimen contained organisms of the same in vitro sensitivity pattern as the first specimen. • Number: 93 randomised, 59 analysed

Komoroski 1999 *(Continued)*

	○ Treatment group: 36 ○ Control group: 23 Exclusion criteria • Pregnancy; antibiotic therapy in the previous 2 weeks; concomitant infection requiring additional antibiotic therapy; known renal or urologic problems that could predispose to a UTI; signs and symptoms of pyelonephritis (ill or toxic appearance, flank pain, costovertebral angle tenderness, or temperature ≥ 38.3°C); history of hypersensitivity to cephalosporins or penicillin; a significant history of gastrointestinal, hematologic, hepatic, psychiatric, or central nervous system disease; history of drug or alcohol abuse; history of sexual abuse as a child; a parent or guardian who was unable to understand or follow instructions; a family situation in which follow-up could not be assured; or refusal to obtain a catheterized sample, if necessary.
Interventions	Treatment group • Single intramuscular ceftriaxone 50 mg/kg (to a maximum of 500 mg) ○ 27 received ceftriaxone (500 mg); 9 received ceftriaxone (250 mg) Control group • TMP-SMX 4-5 mg/kg twice daily for 10 days ○ 22 received TMP-SMX; 1 patient received amoxicillin because of sulfa hypersensitivity
Outcomes	• Persistent bacteriuria (10-30 days following treatment) • Persistent bacteriuria and symptoms (10-30 days following treatment)
Notes	• Nine patients receiving ceftriaxone 250 mg were excluded from this analysis. It appears the study was originally designed to investigate ceftriaxone 250 mg versus control. The ceftriaxone 500 mg groups was added at a later date. When high treatment failures were reported, the 250 mg group was discontinued. The ceftriaxone 250 mg group is not reported as part of this review; using block randomisation, the groups should be of equal size. It does not seem logical that only 9 children were allocated to the ceftriaxone 250 mg group when more than double this number were allocated to the other 2 groups. • Numbers reported in the text do not match the numbers reported in the tables. Numbers reported in tables have been used for this review. • Source of funding: Roche Laboratories Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open label study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It appears that children were randomised to treatment before the inclusion/exclusion criteria were applied. 23 children had urine cultures that showed no significant growth; 8 children had a laboratory or procedural error occurred (e.g., urinalysis obtained but culture not done, organisms in culture not worked up); 3 children did not return for follow-up assessment
Selective reporting (reporting bias)	Unclear risk	Relapse and recurrence were reported, but not in a format suitable for data extraction for this review.

Lidefelt 1991

Methods	• Study design: parallel RCT • Study period: 1986-1988
Participants	Inclusion criteria • Setting/recruitment: emergency department, Sachs' Children's Hospital, Stockholm • Country: Sweden • Children aged less than 3 years to 12 years with symptoms of a UTI (including frequency, dysuria, and painful micturition) and significant bacteriuria defined as ≥ 10^5 cfu/mL in 2 separately voided urine samples. Children were required to have had not more than 2 previous UTIs, and the most recent at least 6 months prior to the start of the study. • Median age: 5 years • Number: treatment group (50); control group (50) • Sex (M/F): 13/87 Exclusion criteria • Signs of upper tract involvement (temperature < 38.5°C, absence of loin pain, ESR < 20 mm/h); more than 2 previous UTIs
Interventions	Treatment group • Single-dose TMP 6 mg/kg Control group • 5-day TMP 3 mg/kg/12 h
Outcomes	• Persistent bacteriuria (7 days following treatment) • Recurrence (> 7 days following treatment)
Notes	• Source of funding: Swedish Medical Council, grant number 19X765, and the Swedish Society of Medicine.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed in groups to which they were assigned
Selective reporting (reporting bias)	Low risk	Planned outcomes were analysed

Malaka-Zafirui 1984

Methods	• Study design: parallel RCT • Study period: NS
Participants	Inclusion criteria • Setting/recruitment: NS • Children aged 8 months to 11.1 years with significant bacteriuria defined as ≥ 10^5 cfu/mL of a single pathogen in 2 consecutive mid-stream urine samples • Number: treatment group (16); control group (16) Exclusion criteria • Hypersensitivity to cephalosporins or penicillins; abnormal hepatic, renal function, or structural anomalies
Interventions	Treatment group • Cefadroxil 25 mg/kg once daily for 10 days Control group • Ampicillin 50 mg/kg/d in 4 divided doses for 10 days
Outcomes	• Persistent bacteriuria (10 days following treatment) • Persistent symptoms (10 days following treatment)
Notes	• Children with pyelonephritis were also included in this study and were reported separately. • Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were analysed in group to which they were assigned
Selective reporting (reporting bias)	Low risk	All planned outcomes were analysed

Mitnik 1985

Methods	• Study design: parallel RCT • Study period: NS

Mitnik 1985 *(Continued)*

Participants	Inclusion criteria • Setting/recruitment: Nephrology clinic of the Hospital Roberto del Rio and the Paediatric Clinic of the Chilean Air Force • Country: Chile • Children aged 2 years to 14 years with symptoms of a UTI (including frequency, dysuria, urgency, foul smelling urine, enuresis and/or haematuria) and significant bacteriuria defined as ≥ 10^5 cfu/mL in voided urine sample, or ≥ 1000 cfu/mL on supra-pubic aspiration. Children were required to have had not more than 2 previous UTIs, and the most recent at least 6 months prior to the start of the study. • Number: treatment group 1 (27); treatment group 2 (35); control group (36) • Sex (M/F): 11/87 Exclusion criteria • Fever > 38°C, low back pain; a history of UTI; anatomical abnormalities; received antibiotics in the week prior to the study.
Interventions	Treatment group 1 • 3-day antibiotics Treatment group 2 • 5-day antibiotics Control group • 10-day antibiotics Children were administered a first generation cephalosporin, nitrofurantoin or TMP-SMX depending on the sensitivity of the organism cultured
Outcomes	• Recurrence (at 2-3 months)
Notes	• The 3-day and 5-day interventions were combined into one group and compared to the 10-day control • Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients analysed in group to which they were assigned
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported

Principi 1990

Methods	• Study design: parallel RCT • Study period: NS
Participants	Inclusion criteria • Setting/recruitment: outpatients authors were from various university hospitals • Country: Italy • Children aged 1 month to 16 years with a lower UTI. Significant bacteriuria defined as > 10^5 cfu/mL of a single pathogen in 2 clean catch or catheterised urine samples. Lower UTI was defined as absence of fever, ESR < 25 mm/L/h and CRP < 20 µg/mL • Number: treatment group (71); control group (64) • Sex (M/F): 45/90 Exclusion criteria • Renal failure
Interventions	Treatment group • Single-dose fosfomycin trometamol (2 g orally; 1 g in children < 1 year) Control group • Single-dose netilmicin (5 mg/kg intramuscularly)
Outcomes	• Persistent bacteriuria (2-4 days following treatment) • Recurrence (up to 30 days following treatment)
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients analysed in group to which they were assigned
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported

Sanchez 1990

Methods	• Study design: parallel RCT

Sanchez 1990 *(Continued)*

	• Study period: NS
Participants	Inclusion criteria • Setting/recruitment: emergency department, Hospital Materno-Infantil Vall d'Hebron, Barcelona • Country: Spain • Children aged 8 months to 11.1 years with significant bacteriuria defined as ≥ 10^5 cfu/mL of a single pathogen in 2 consecutive mid-stream urine samples. • Number: 37 Exclusion criteria • Children aged less than 4 months, with a fever of >38.5°C, back pain or mass, malaise, duration of symptoms longer than one week, vomiting, received antibiotics in the previous 2 weeks, underlying disease involving immunosuppression, or known urinary tract malformation were excluded
Interventions	• Children received amoxicillin, amoxicillin + clavulanic acid, cephalexin, TMP or co-trimoxazole at standard doses for 7 days.
Outcomes	• Persistent bacteriuria (2-3 days following treatment)
Notes	• This study was published as an abstract • Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only, not enough detail provided
Selective reporting (reporting bias)	Unclear risk	Abstract only, not enough detail provided

Shapiro 1981

Methods	• Study design: parallel RCT • Study period: NS
Participants	Inclusion criteria • Setting/recruitment: emergency department, Children's Hospital of Pittsburgh • Country: USA

Shapiro 1981 *(Continued)*

	• Girls aged 2 to 18 years with symptoms of a UTI (including frequency, dysuria and/or urgency) and significant bacteriuria defined as ≥ 10^5 cfu/mL in 2 clean catch urine samples, or ≥ 1000 cfu/mL on supra-pubic aspiration.
	• Mean age: 5.6 years
	• Number: 37 randomised, 35 analysed
	  ○ Treatment group: 18
	  ○ Control group: 17
	
	Exclusion criteria
	
	• Clinical evidence of upper UTI (fever > 38°C and/or flank pain); known anatomic or functional urinary tract abnormality; currently receiving antibiotics; history of penicillin allergy

Interventions	Treatment group • Single-dose amoxicillin 50 mg/kg (to a maximum of 2.5 g) Control group • 10-day amoxicillin 40 mg/kg/d in 3 divided doses (to a maximum of 500 mg/dose)
Outcomes	• Persistent bacteriuria (2 days following treatment) • Recurrence (within 3 months following treatment)
Notes	Source of funding: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Patient and physician
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Two children were excluded from analyses because the second urine culture was negative.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported

Stahl 1984

Methods	• Study design: parallel RCT • Study period: NS
Participants	Inclusion criteria • Setting/recruitment: outpatients and emergency department, Children's Hospital of Philadelphia and St Christopher's Hospital for Children, Philadelphia • Country: USA

Stahl 1984 *(Continued)*

	• Girls aged 2 to 17 years with symptoms of a UTI (including frequency, dysuria, urgency, enuresis, suprapubic pain, or haematuria with pyuria) and significant bacteriuria defined as ≥ 10^5 cfu/mL of a single organism in 2 sequential clean catch urine samples.
	• Median age: 4.75 years
	• Number of participants: 36 randomised, 26 analysed
	  ○ Treatment group: 10
	  ○ Control group: 16
	
	Exclusion criteria
	
	• Signs or symptoms of upper UTI (temperature > 38.9°C, flank pain, costovertebral angle tenderness or toxic appearance); known renal or urologic disorder; history of penicillin allergy; received antibiotics in the previous 2 weeks

Interventions	Treatment group • Single-dose amoxicillin 50 mg/kg orally (to a maximum of 3 g) Control group • 10-day amoxicillin 30 mg/kg/d in 3 divided doses (to a maximum of 250 mg/dose)
Outcomes	• Persistent bacteriuria (2-4 days following treatment) • Reinfection (> 2 weeks following treatment)
Notes	• Data on re-infection could not be used from this study as the definition included both a positive culture more than 2 weeks following therapy of any organism (defined as recurrence by this review) or an infection caused by a different organism (defined as re-infection by this review). These results were presented together. • Source of funding: Beecham Laboratories, Bristol, Tennessee

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Six girls were lost to follow-up, in 3 girls the 2nd urine culture was negative and 1 girl had received antibiotics within the previous 2 weeks. One girl in the single-dose group had an amoxicillin resistant organism and was switched to 10 days TMP-SMX and then followed in the conventional therapy group.
Selective reporting (reporting bias)	Unclear risk	All planned outcomes were reported

Wallen 1983

Methods	• Study design: parallel RCT

Wallen 1983 *(Continued)*

	• Study period: NS

Participants	Inclusion criteria
	• Setting/recruitment: outpatients, The Children's Memorial Hospital, Chicago
	• Country: USA
	• Girls aged 1 year to 12 years with suspected UTI and significant bacteriuria defined as ≥ 10^5 cfu/mL *E. coli* organisms in 2 clean catch or urine collection bag samples.
	• Median age: 5.45 years
	• Number: 54 randomised, 49 analysed
	  ○ Treatment group: 26
	  ○ Control group: 25
	Exclusion criteria
	• Clinical symptoms of pyelonephritis (including fever > 38.3°C, flank pain, chills, ESR >21 mm/h); previous UTIs; antibiotic use during the week prior to the study; known urinary tract abnormalities

Interventions	Treatment group • Single-dose intramuscular amikacin sulfate 7.5 mg/kg (to a maximum of 240 mg) Control group • 10-day sulfisoxazole 150 mg/kg/day in 4 divided doses
Outcomes	• Persistent bacteriuria (2-4 days following treatment) • Recurrence (30-40 days following treatment)
Notes	• Re-infection rates were presented, but were only available for the single-dose amikacin group; these rates have not been reported in this review. • Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	At the 2-4 day follow-up, 6 girls were lost to follow-up. By the 30-40 day follow-up, 10 girls were lost to follow-up.
Selective reporting (reporting bias)	Low risk	All planned outcomes were reported

BUN - blood urea nitrogen; CRP - C-reactive protein; ESR - erythrocyte sedimentation rate; NS - not stated; SCr - serum creatinine; SMX - sulfamethoxazole; TMP - trimethoprim; UTI - urinary tract infection

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

Study	Reason for exclusion
Adam 1982	Children with pre-existing conditions, and who have symptoms of pyelonephritis are not reported separately from children with lower UTI
Anttila 1980	Not RCT
Arap 1983	Half of included children had fever and were not reported separately from those without
Arguedas 2009	Children had complicated UTI
Arrieta 2001	Included children had pyelonephritis
Asscher 1973	Not an RCT; screening study only
Bahur 2003	Included children had fever
Bailey 1977	Almost half of the included children had known renal impairment
Baker 2001	Included children were required to be febrile (i.e. systemic illness).
Bakkaloglu 1996	Included children had pyelonephritis
Belet 2004	Prophylaxis for preventing recurrence
Bose 1974	More than half of the included children had pre-existing renal abnormalities.
Bourillon 1994	Included children had pyelonephritis
Caparelli 1983	Some children had pyelonephritis; unclear how many
Carapetis 2001	Most included children had systemic symptoms
Careddu 1987	Study is conducted in symptomatic and asymptomatic children, but proportion of each is unknown. Also, 11/51 children had known renal abnormalities.
Carlsen 1985	Prophylactic antibiotics
Chibante 1994	Some children had complicated UTI and were not presented separately from those with lower UTI
Chong 2003	Children had systemic symptoms
Chrapowicki 1975	Included children had pyelonephritis
Clemente 1994	Included children had fever
Dagan 1992	Majority of included children had fever
De Garate 1988	One third of included children had cystopyelitis or pyelonephritis and were not reported separately from those without
Ellerstein 1977	Not enough information reported on symptoms to know whether children had lower UTI; 5/34 had reflux and 3/34 had abdominal pain, but other symptoms were not reported.
Elo 1975	Two thirds of included children had renal abnormalities

Study	Reason for exclusion
Feldman 1975	Some children had fever and were not reported separately from those without
Fischbach 1989	Included children had signs of systemic illness (fever)
Francois 1995	Included children had pyelonephritis
Francoise 1997	Included children had pyelonephritis
Fuji 1987	Some children had pyelonephritis and were not reported separately from children without.
Gaudreault 1992	Comparison of short versus standard duration antibiotic for lower UTI - included in Michael 2003
Ginsburg 1982	Approximately 1/3 of included children had fever and were not reported separately from those without
Gok 2001	Approximately 1/3 of included children had pyelonephritis and over half had urinary tract abnormalities
Goldberg 1977	Children with fever not reported separately from children without.
Gonzalez 1985	35% of included children had fever and were not reported separately from those without
Goos 2006	Not a RCT, or quasi-RCT
Goos 2007	Not RCT
Goszczyk 2000	Children received 3 months antibiotic treatment for preventing recurrence.
Gould 1975	Unclear if participants were children. Included participants had prostatitis, acute cystitis, urethritis, and/or trigonitis but results were not reported separately.
Granados 1998	Prophylactic antibiotics
Hansen 1981	Approximately half of children presented with fever and were not reported separately from children without fever.
Hayashida 1970	Some children had pyelonephritis and were not reported separately from those without
Helin 1981	Comparison of short versus standard duration antibiotic for lower UTI - included in Michael 2003
Hoberman 1999	Included children were required to have a temperature of > 38.3°C
Howard 1978	Just under half of the included children had fever and approximately 65% had symptoms of malaise
Johnson 1993	Comparison of short versus standard duration antibiotic for lower UTI - included in Michael 2003
Jojart 1991	Comparison of short versus standard duration antibiotic for lower UTI - included in Michael 2003
Kenda 1995	Not RCT
Khan 1987	Not RCT
Kornberg 1994	Comparison of short versus standard duration antibiotic for lower UTI - included in Michael 2003

Study	Reason for exclusion
Krepler 1976	Included children had pyelonephritis
Lohr 1981	Comparison of short versus standard duration antibiotic for lower UTI - included in Michael 2003
Lubitz 1984	Symptoms not reported. 35% of included children had renal abnormalities
Madrigal 1988	Comparison of short versus standard duration antibiotic for lower UTI - included in Michael 2003
Marild 2009	Included children were required to have fever
McCracken 1981	> 20% of children had fever, abdominal/flank pain and costovertebral tenderness indicating pyelonephritis.
Moe 1977	Not all included children had bacteriologically proven UTI
Montini 2007	Children had pyelonephritis
Nolan 1989	Half of the included children had fever, loin pain and/or back pain
Noorbakhsh 2004	Included children had pyelonephritis
Olbing 1971	Some children had renal abnormalities; although the results refer to patients with and without abnormalities, no numbers are included so data cannot be extracted.
Palcoux 1986	Half of included children had known renal abnormalities
Pitt 1982	More than half of the included children had abdominal pain and/or fever
Pylkkanen 1981	Compared 10-day treatment with 42-day treatment in children
Repetto 1984	Children with fever were not analysed separately from children without fever
Rodriguez 1983	Included children had fever
Ruberto 1984	52% of children had fever and were not reported separately from those without
Russo 1989	Majority of included children had fever
Schach 1972	Most children received concomitant surgical therapy
Sember 1985	Some patients had fever and/or lumber pain and were not reported separately from patients without.
Stansfeld 1975	Symptoms not reported. Approximately half of included children had reflux, but grade of reflux was not reported.
Stogmann 1983	Most included children had fever
Sullivan 1980	No symptoms of UTI reported. Bacteriological definition of UTI only.
Tambic 1992	As per Michael 2003. Study was excluded because significantly more patients (32/59) with pyelonephritis were Included in the 7-day group compared with 3-day group (11/58) ($Chi^2 = 15.65$, $df = 1$; $P < 0.001$), which strongly suggested non-random allocation.
Tapaneya 1999	Included children were required to have fever

Study	Reason for exclusion
Tong 2005	Some children had pyelonephritis but were not reported separately from those without
Toporovski 1988	Included children presented with fever
Varese 1987	One third of included children had known renal abnormalities and are not presented separately from those without
Vlatkovic 1972	Included children had pyelonephritis
Vlatkovic 1974	Included children had pyelonephritis
Weber 1982	More than half of the included children had fever and were not reported separately from those without
Wientzen 1979	Comparison of short versus standard duration antibiotic for lower UTI - included in Michael 2003
Zaki 1986	Comparison of short versus standard duration antibiotic for lower UTI - included in Michael 2003

randomised controlled trial- RCT; UTI - urinary tract infection

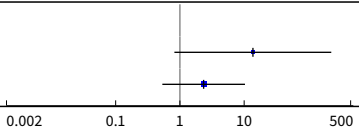
DATA AND ANALYSES

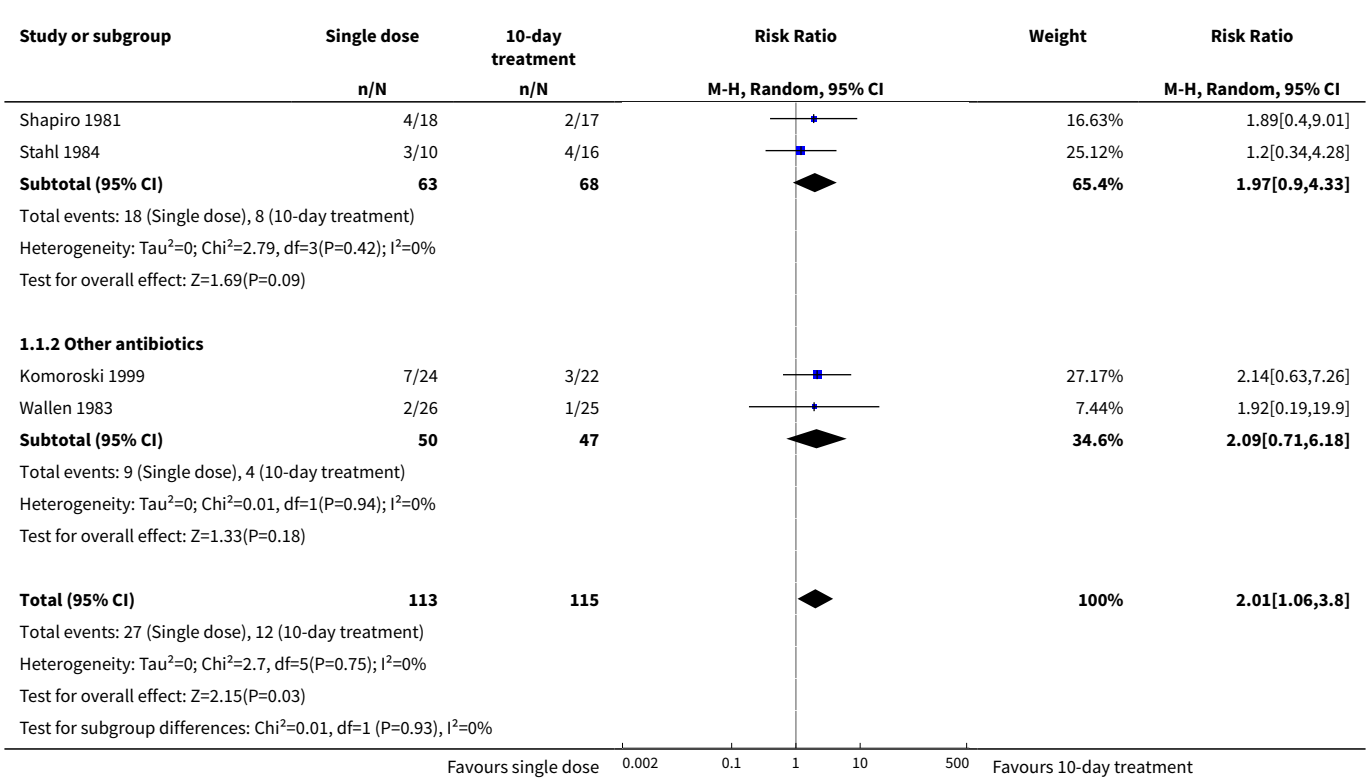
Comparison 1. Single-dose versus conventional 10-day treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent bacteriuria	6	228	Risk Ratio (M-H, Random, 95% CI)	2.01 [1.06, 3.80]
1.1 Amoxicillin	4	131	Risk Ratio (M-H, Random, 95% CI)	1.97 [0.90, 4.33]
1.2 Other antibiotics	2	97	Risk Ratio (M-H, Random, 95% CI)	2.09 [0.71, 6.18]
2 Persistent symptoms	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Recurrence	2	79	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.55, 3.50]
4 Persistent bacteriuria and symptoms	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

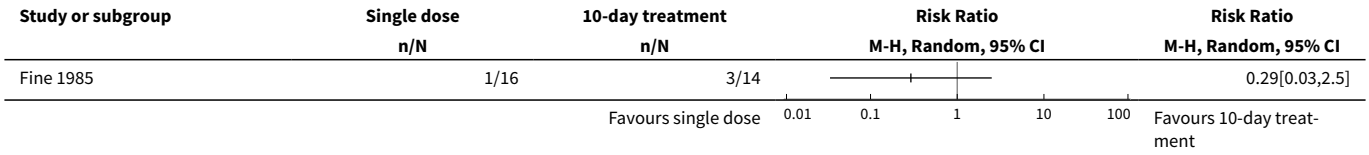
Analysis 1.1. Comparison 1 Single-dose versus conventional 10-day treatment, Outcome 1 Persistent bacteriuria.

Study or subgroup	Single dose	10-day treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.1.1 Amoxicillin					
Avner 1983	6/19	0/20		5.14%	13.65[0.82,226.84]
Fine 1985	5/16	2/15		18.52%	2.34[0.53,10.3]

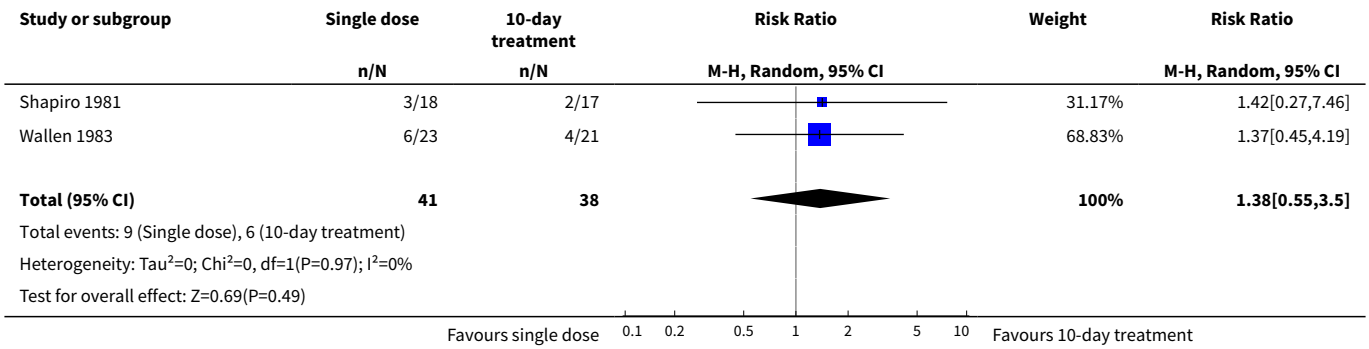




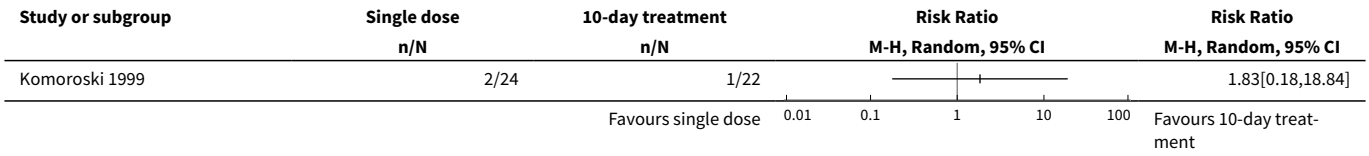
Analysis 1.2. Comparison 1 Single-dose versus conventional 10-day treatment, Outcome 2 Persistent symptoms.



Analysis 1.3. Comparison 1 Single-dose versus conventional 10-day treatment, Outcome 3 Recurrence.



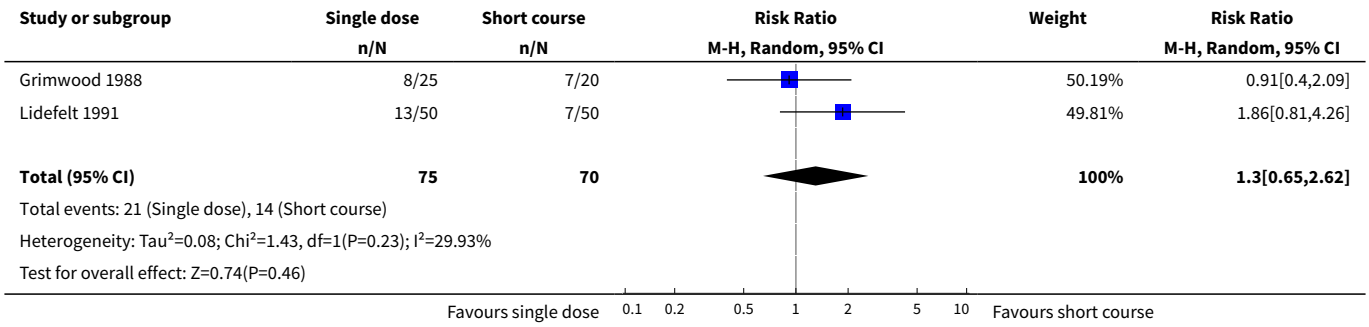
Analysis 1.4. Comparison 1 Single-dose versus conventional 10-day treatment, Outcome 4 Persistent bacteriuria and symptoms.



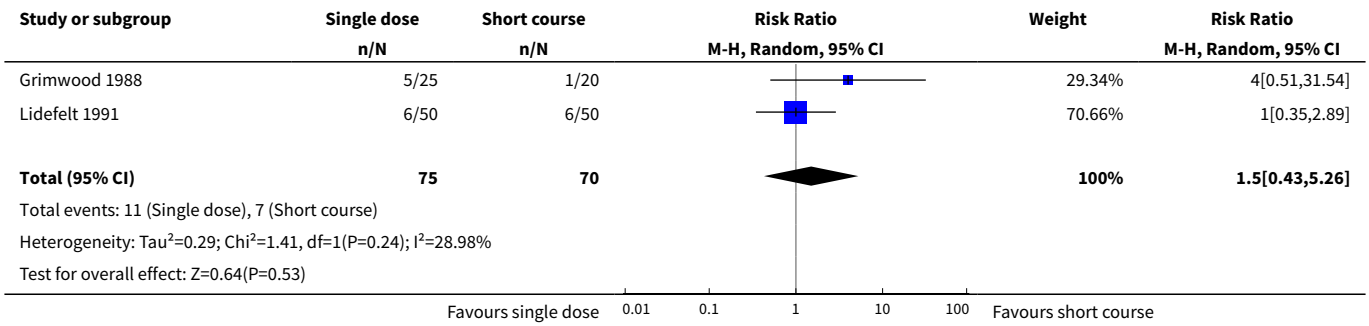
Comparison 2. Single-dose versus short-course (3-7 days) treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent bacteriuria	2	145	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.65, 2.62]
2 Recurrence	2	145	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.43, 5.26]
3 Re-infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Single-dose versus short-course (3-7 days) treatment, Outcome 1 Persistent bacteriuria.



Analysis 2.2. Comparison 2 Single-dose versus short-course (3-7 days) treatment, Outcome 2 Recurrence.



Analysis 2.3. Comparison 2 Single-dose versus short-course (3-7 days) treatment, Outcome 3 Re-infection.

Study or subgroup	Single dose n/N	Short course n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Grimwood 1988	1/25	5/20		0.16[0.02,1.26]

Favours single dose 0.01 0.1 1 10 100 Favours short course

Comparison 3. Short-course (3-7 days) versus long-course (10-14 days) treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent bacteriuria	3	265	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.67, 1.76]
2 Recurrence	4	328	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.74, 2.13]
3 Re-infection	2	211	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.44, 1.74]

Analysis 3.1. Comparison 3 Short-course (3-7 days) versus long-course (10-14 days) treatment, Outcome 1 Persistent bacteriuria.

Study or subgroup	Short course (3-7 days) n/N	Long course (10-14 days) n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
CSG 1991	23/90	18/78		79.8%	1.11[0.65,1.89]
Helin 1984	2/19	1/24		4.26%	2.53[0.25,25.8]
Khan 1981	4/27	5/27		15.94%	0.8[0.24,2.66]
Total (95% CI)	**136**	**129**		**100%**	**1.09[0.67,1.76]**

Total events: 29 (Short course (3-7 days)), 24 (Long course (10-14 days))
Heterogeneity: Tau^2=0; Chi^2=0.76, df=2(P=0.68); I^2=0%
Test for overall effect: Z=0.35(P=0.73)

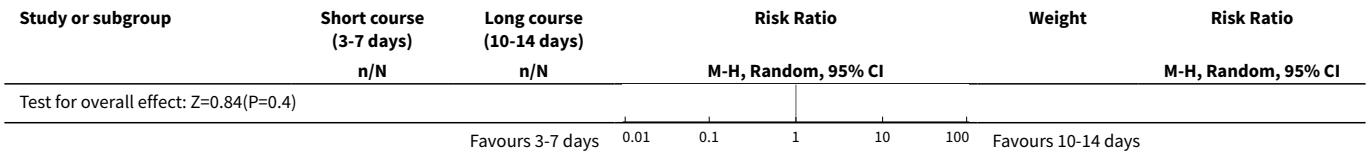
Favours 3-7 days 0.01 0.1 1 10 100 Favours 10-14 days

Analysis 3.2. Comparison 3 Short-course (3-7 days) versus long-course (10-14 days) treatment, Outcome 2 Recurrence.

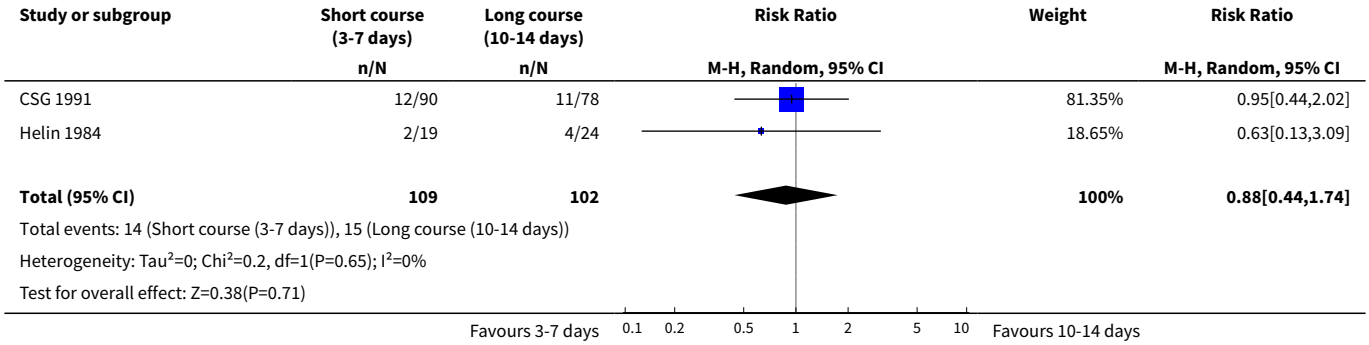
Study or subgroup	Short course (3-7 days) n/N	Long course (10-14 days) n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
CSG 1991	11/90	7/78		34.83%	1.36[0.55,3.34]
Helin 1984	2/19	1/24		5.2%	2.53[0.25,25.8]
Khan 1981	4/27	3/27		14.35%	1.33[0.33,5.4]
Mitnik 1985	8/27	10/36		45.62%	1.07[0.49,2.34]
Total (95% CI)	**163**	**165**		**100%**	**1.25[0.74,2.13]**

Total events: 25 (Short course (3-7 days)), 21 (Long course (10-14 days))
Heterogeneity: Tau^2=0; Chi^2=0.56, df=3(P=0.91); I^2=0%

Favours 3-7 days 0.01 0.1 1 10 100 Favours 10-14 days



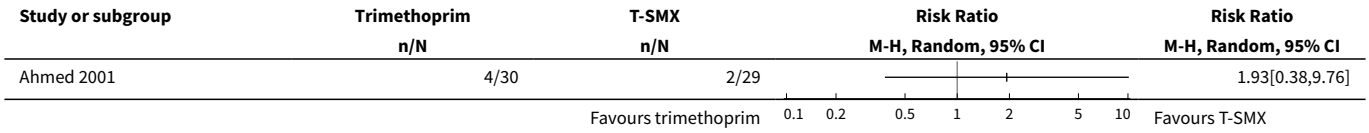
Analysis 3.3. Comparison 3 Short-course (3-7 days) versus long-course (10-14 days) treatment, Outcome 3 Re-infection.



Comparison 4. Trimethoprim (10 days) versus trimethoprim+sulfamethoxazole (10 days)

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

Analysis 4.1. Comparison 4 Trimethoprim (10 days) versus trimethoprim +sulfamethoxazole (10 days), Outcome 1 Persistent bacteriuria.



Analysis 4.2. Comparison 4 Trimethoprim (10 days) versus trimethoprim +sulfamethoxazole (10 days), Outcome 2 Persistent symptoms.

Study or subgroup	Trimethoprim n/N	T-SMX n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ahmed 2001	2/30	0/29		4.84[0.24,96.66]

Favours trimethoprim 0.01 0.1 1 10 100 Favours T-SMX

Analysis 4.3. Comparison 4 Trimethoprim (10 days) versus trimethoprim+sulfamethoxazole (10 days), Outcome 3 Recurrence.

Study or subgroup	Trimethoprim n/N	T-SMX n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ahmed 2001	1/30	0/29		2.9[0.12,68.5]

Favours trimethoprim 0.01 0.1 1 10 100 Favours T-SMX

Comparison 5. Cefadroxil (10 days) versus ampicillin (10 days)

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

Analysis 5.1. Comparison 5 Cefadroxil (10 days) versus ampicillin (10 days), Outcome 1 Persistent bacteriuria.

Study or subgroup	Cefadroxil n/N	Ampicillin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Malaka-Zafirui 1984	0/16	1/16		0.33[0.01,7.62]

Favours cefadroxil 0.01 0.1 1 10 100 Favours ampicillin

Analysis 5.2. Comparison 5 Cefadroxil (10 days) versus ampicillin (10 days), Outcome 2 Persistent symptoms.

Study or subgroup	Cefadroxil n/N	Ampicillin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Malaka-Zafirui 1984	0/16	1/16		0.33[0.01,7.62]

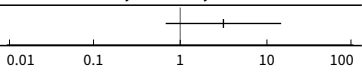
Favours cefadroxil 0.01 0.1 1 10 100 Favours ampicillin

Comparison 6. Single-dose fosfomycin versus single-dose netilmicin

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

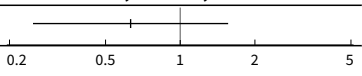
Analysis 6.1. Comparison 6 Single-dose fosfomycin versus single-dose netilmicin, Outcome 1 Persistent bacteriuria.

Study or subgroup	Fosfomycin n/N	Netilmicin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Principi 1990	7/71	2/64		3.15[0.68,14.64]



Analysis 6.2. Comparison 6 Single-dose fosfomycin versus single-dose netilmicin, Outcome 2 Recurrence.

Study or subgroup	Fosfomycin n/N	Netilmicin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Principi 1990	7/71	10/64		0.63[0.26,1.56]



APPENDICES

Appendix 1. Electronic search strategy

Database	Search terms used
CENTRAL	1. child*:ti,ab,kw 2. (infant* or babies or neonat* or newborn* or toddler*):ti,ab,kw 3. (adolescen* or pubert* or pubesc* or prepubert* or prepubesc* or juvenile* or youth* or teen*):ti,ab,kw 4. (pediatr* or paediatr*):ti,ab,kw 5. (boys or girls):ti,ab,kw 6. (#1 OR #2 OR #3 OR #4 OR #5) 7. MeSH descriptor Urinary Tract Infections explode all trees 8. MeSH descriptor Cystitis explode all trees 9. MeSH descriptor Pyelonephritis, this term only 10.urinary next tract next infection*:kw 11.cystitis:ti,ab,kw 12.pyelonephr*:ti,ab,kw 13.bacteriuria*:ti,ab,kw 14.(pyuria or pyuric or pyurias):ti,ab,kw 15.(uti or utis):ti,ab,kw

(Continued)

16.((bladder* or genitourin* or renal or ureter* or ureth* or urin* or urol* or urogen*) near5 (infect* or bacteria* or microbiol*)):ti,ab
17.(bladder* near5 (ulcer* or ulcus)):ti,ab
18.(#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)
19.(#6 AND #18)
20.SR-RENAL
21.(#19 AND NOT 20)
22.Anti-infective next agents:kw
23.Antiinfective next agent:kw
24.MeSH descriptor Anti-Infective Agents, Urinary explode all trees
25.antibiotic next agent:kw
26.antibiotic*:ti,ab
27.bacteriocid*:ti,ab
28.((antimycobacterial* or antibacterial* or bacteriocid*) near2 agent*):ti,ab
29.((antiseptic* or anti-infective* or antiinfective*) near5 urin*):ti,ab
30.penicillin*:ti,ab,kw
31.amox*cil*:ti,ab,kw
32.amoxil*:ti,ab,kw
33.augmentin*:ti,ab,kw
34.ampicillin*:ti,ab,kw
35.penbritin*:ti,ab,kw
36.ce*adrox*:ti,ab,kw
37.ce*alexin*:ti,ab,kw
38.cefaclor*:ti,ab,kw
39.ceporex*:ti,ab,kw
40.keflex*:ti,ab,kw
41.ce*ixim*:ti,ab,kw
42.suprax*ti,ab,kw
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55.ceftriaxon*:ti,ab,kw
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57.cefuroxim*:ti,ab,kw
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59.zinnat*:ti,ab,kw
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62.genticin*:ti,ab,kw
63.methenamin*:ti,ab,kw
64.hexamin*:ti,ab,kw
65.hiprex:ti,ab,kw

(Continued)

66.nitrofuranto*:ti,ab,kw
67.furadantin*:ti,ab,kw
68.macrodantin*:ti,ab,kw
69.trimethoprim*:ti,ab,kw
70.cotrimoxazole*:ti,ab,kw
71.monotrim*:ti,ab,kw
72.amdinocillin*:ti,ab,kw
73.mecillinam*:ti,ab,kw
74.selexid*:ti,ab,kw
75.amikacin*:ti,ab,kw
76.aminoglycosid*:ti,ab,kw
77.aminoglucoside*:ti,ab,kw
78.tobramycin*:ti,ab,kw
79.nebcin*:ti,ab,kw
80.tobi:ti,ab,kw
81.quinolone*:ti,ab,kw
82."4-quinolones":kw
83."4 Quinolone Derivative":kw
84.netilmicin*:ti,ab,kw
85.netillin*:ti,ab,kw
86.(#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85)
87.(#21 AND #86)

MEDLINE (OVID SP)

1. exp Child/
2. exp Infant/
3. Adolescent/
4. Puberty/
5. child$.tw.
6. (pediatric or paediatric).tw.
7. (boys or girls).tw.
8. (infant$ or babies or neonat$ or newborn$ or toddler$).tw.
9. (adolescen$ or pubert$ or pubesc$ or prepubert$ or prepubesc$ or juvenile$ or youth$ or teen $).tw.
10. or/1-9
11. exp Urinary Tract Infections/
12. exp Cystitis/
13. Pyelonephritis/
14. (uti or utis).tw.
15. bacteriuria$.tw.
16. (pyuria or pyuric or pyurias).tw.
17. cystitis.tw.
18. (bladder$ adj5 (ulcer$ or ulcus)).tw.
19. ((bladder$ or genitourin$ or renal or ureter$ or ureth$ or urin$ or urolog$ or urogen$) adj5 (infect$ or bacteria$ or microbiol$)).tw.
20. pyelonephr$.tw.
21. pyelocystit$.tw.
22. or/11-21
23. and/10,22

(Continued)

24.Anti-Infective Agents/
25.Anti-Bacterial Agents/
26.exp Anti-Infective Agents, Urinary/
27.antibiotic$.tw.
28.bacteriocid$.tw.
29.antibacterial$.tw.
30.antimycobacterial$.tw.
31.antiseptic$.tw.
32.anti?infective$.tw.
33.anti-infective.tw.
34.Penicillins/
35.penicillin$.tw.
36.Amoxicillin/
37.amoxicil$.tw.
38.amoxycil$.tw.
39.amoxil$.tw.
40.Amoxicillin-Potassium Clavulanate Combination/
41.augmentin$.tw.
42.Ampicillin/
43.ampicillin$.tw.
44.penbritin$.tw.
45.Cefadroxil/
46.cephadroxil$.tw.
47.cefadroxil$.tw.
48.cephadrox$.tw.
49.Cephalexin/
50.cephalexin$.tw.
51.cefalexin$.tw.
52.cefaclor$.tw.
53.ceporex$.tw.
54.keflex$.tw.
55.Cefixime/
56.cefixim$.tw.
57.cephixim$.tw.
58.suprax$.tw.
59.Cefotaxime/
60.cefotaxim$.tw.
61.cephotaxim$.tw.
62.claforan$.tw.
63.klaforan$.tw.
64.Cephalosporins/
65.cefpirome$.tw.
66.Ceftizoxime/
67.ceftizoxim$.tw.
68.cefpodoxim$.tw.
69.orelox$.tw.
70.Cephradine/
71.cefradin$.tw.
72.velosef$.tw.
73.Ceftazidime/
74.ceftazidim$.tw.

(Continued)

	75.fortum$.tw. 76.Ceftriaxone/ 77.ceftriaxon$.tw. 78.rocephin$.tw. 79.Cefuroxime/ 80.cefuroxim.tw. 81.zinacef$.tw. 82.zinnat$.tw. 83.Gentamicins/ 84.gentamicin$.tw. 85.cidomycin$.tw. 86.genticin$.tw. 87.Methenamine/ 88.methenamin$.tw. 89.hexamine$.tw. 90.hiprex.tw. 91.Nitrofurantoin/ 92.nitrofuranto$.tw. 93.furadantin$.tw. 94.macrodantin$.tw. 95.Trimethoprim/ 96.Trimethoprim-Sulfamethoxazole Combination/ 97.trimethoprim$.tw. 98.monotrim$.tw. 99.Amdinocillin/ 100.amdinocillin$.tw. 101.mecillinam$.tw. 102.selexid$.tw. 103.Amikacin/ 104.amikacin.tw. 105.Aminoglycosides/ 106.aminoglycoside$.tw. 107.aminoglucoside$.tw. 108.Tobramycin/ 109.tobramycin$.tw. 110.nebcin$.tw. 111.tobi.tw. 112.Quinolones/ 113.4-Quinolones/ 114.quinolone$.tw. 115.Netilmicin/ 116.netilmicin$.tw. 117.netillin$.tw. 118.or/24-117 119.and/23,118
EMBASE (OVID SP)	1. exp Child/ 2. exp Newborn/ 3. Adolescent/ 4. exp Adolescence/ 5. exp Childhood/ 6. child$.tw.

(Continued)

7. (pediatr$ or paediatr$).tw.
8. (boys or girls).tw.
9. (infant$ or babies or neonat$ or newborn$ or toddler$).tw.
10. (adolescen$ or pubert$ or pubesc$ or prepubert$ or prepubesc$ or juvenile$ or youth$ or teen $).tw.
11. or/1-10
12. exp Urinary Tract Infection/
13. exp Cystitis/
14. exp Pyelonephritis/
15. Bacteriuria/
16. Pyuria/
17. (uti or utis).tw.
18. bacteriuria$.tw.
19. (pyuria or pyuric or pyurias).tw.
20. cystitis.tw.
21. (bladder$ adj5 (ulcer$ or ulcus)).tw.
22. ((bladder$ or genitourin$ or renal or ureter$ or ureth$ or urin$ or urolog$ or urogen$) adj5 (infect$ or bacteria$ or microbiol$)).tw.
23. pyelonephr$.tw.
24. pyelocystit$.tw.
25. or/12-24
26. and/11,25
27. Antiinfective Agent/
28. Antibiotic Agent/
29. antibiotic$.tw.
30. bacteriocide$.tw.
31. ((antimycobacterial$ or antibacterial$ or bacteriocid$) adj2 agent$).tw.
32. Penicillin Derivitive/ or Penicillin G/
33. penicillin.tw.
34. exp Urinary Tract Antiinfective Agent/
35. ((antiseptic$ or anti?infective$) adj5 urin$).tw.
36. Amoxicillin/
37. amoxicil$.tw.
38. amoxycil$.tw.
39. amoxil$.tw.
40. Amoxicillin Plus Clavulanic Acid/
41. augmentin$.tw.
42. Ampicillin/
43. ampicillin$.tw.
44. penbritin$.tw.
45. Cefadroxil/
46. cefadroxil$.tw.
47. cephadrox$.tw.
48. Cefalexin/
49. cephalexin$.tw.
50. cefalexin$.tw.
51. cefaclor$.tw.
52. ceporex$.tw.
53. keflex$.tw.
54. Cefixime/
55. cefixim$.tw.
56. cephixim$.tw.

(Continued)

57.suprax$.tw.
58.Cefotaxime/
59.cefotaxim$.tw.
60.cephotaxim$.tw.
61.claforan$.tw.
62.klaforan$.tw.
63.Cephalosporin Derivative/
64.cefpirome$.tw.
65.Ceftizoxime/
66.ceftizoxim$.tw.
67.cefpodoxim$.tw.
68.orelox$.tw.
69.Cefradine/
70.cefradin$.tw.
71.cephradin$.tw.
72.velosef$.tw.
73.Ceftazidime/
74.ceftazidim$.tw.
75.fortum$.tw.
76.Ceftriaxone/
77.ceftriaxon$.tw.
78.rocephin$.tw.
79.Cefuroxime/
80.cefuroxim.tw.
81.zinacef$.tw.
82.zinnat$.tw.
83.Gentamicin/
84.gentamicin$.tw.
85.cidomycin$.tw.
86.genticin$.tw.
87.Methenamine/
88.methenamin$.tw.
89.hexamine$.tw.
90.hiprex.tw.
91.Nitrofurantoin/
92.nitrofuranto$.tw.
93.furadantin$.tw.
94.macrodantin$.tw.
95.Trimethoprim/
96.Cotrimoxazole/
97.trimethoprim$.tw.
98.monotrim$.tw.
99.Mecillinam/
100.mecillinam$.tw.
101.amdinocillin$.tw.
102.selexid$.tw.
103.Amikacin/
104.amikacin.tw.
105.Aminoglycoside/
106.aminoglycoside$.tw.
107.aminoglucoside$.tw.

(Continued)

108	Tobramycin/
109	Tobramycin Sulfate/
110	tobramycin$.tw.
111	nebcin$.tw.
112	tobi.tw.
113	Quinolone/
114	4 Quinolone Derivative/
115	quinolone$.tw.
116	Netilmicin/
117	netilmicin$.tw.
118	netillin$.tw.
119	or/27-118
120	and/26,119

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement

(Continued)

Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
22 July 2014	Amended	Minor copy edit of study name

HISTORY

Protocol first published: Issue 4, 2007
Review first published: Issue 8, 2012

Date	Event	Description
10 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Writing of protocol and review: AF, RM
- Screening of titles and abstracts: AF, RM
- Assessment for inclusion: AF, RM
- Quality assessment: AF, RM
- Data extraction: AF, RM
- Data entry into RevMan: AF
- Data analysis: AF, RM
- Disagreement resolution: ML, KT

DECLARATIONS OF INTEREST

- Anita Fitzgerald: Some of this work was undertaken when all authors were employed by, or were advisor's to, the National Collaborating Centre for Women's and Children's Health which received funding from NICE. The views expressed in this publication are those of the authors and not necessarily those of NICE.
- Monica Lakhanpaul: I was the Clinical Director at the National Collaborating Centre for Women's Health and led the development of the NICE Urinary Tract Infection Guideline. I am no longer the Clincial Director but remain on the NCC-WCH board and i am a NICE Fellow and member of the NHS evidence advisory team.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Re-defined the outcome of recurrence to include re-infection; we used the definition recurrence (growth of original bacteria) and re-infection (growth of new bacteria)
- In some studies urine samples were collected using non-invasive methods (clean-catch, urine collection bag or pad) but if urine was unobtainable, several studies included the option of a supra-pubic aspiration or catheter samples. We included studies that collected urine using supra-pubic aspiration or catheters, as the difficulties in collecting urine from children, particularly infants can be problematic.
- We initially defined recurrence as at least three episodes of cystitis/lower UTI; however in the included studies any recurrence was reported. We therefore included data on any recurrence.
- Adverse effects were to be tabulated - this was not performed.
- Risk of bias assessment tool has replaced the quality assessment checklist.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant; Infant, Newborn