ClinicalEvidence

Urinary tract infection in children

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ABSTRACT

INTRODUCTION: Up to 11.3% of girls and 3.6% of boys will have had a urinary tract infection (UTI) by the age of 16 years, and recurrence of infection is common. Vesicoureteric reflux is identified in up to 40% of children being investigated for a first UTI, and is a risk factor for, but weak predictor of, renal parenchymal defects. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatment of acute urinary tract infection in children? What are the effects of interventions to prevent recurrence? We searched: Medline, Embase, The Cochrane Library, and other important databases up to July 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 25 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: antibiotics (short initial intravenous antibiotics, long initial intravenous antibiotics, initial oral antibiotics, single-dose or single-day courses of oral antibiotics, short courses of oral antibiotics, long courses of oral antibiotics, immediate empirical antibiotics, delayed antibiotics, prolonged delay of antibiotics, prophylactic antibiotics); immunotherapy; surgical correction of minor functional abnormalities; and surgical correction of moderate to severe vesicoureteric reflux.

QUESTIONS

INTERVENTIONS

Footnote

*Based on consensus. RCTs would be considered unethical.

Key points

- Up to 11.3% of girls and 3.6% of boys will have had a UTI by the age of 16 years, and recurrence of infection is common.

  Vesicoureteric reflux is identified in up to 40% of children being investigated for a first UTI, and it is a risk factor for, but weak predictor of, renal scarring.

  Renal parenchymal defects occur in 5% to 15% of children within 1 to 2 years of their first presentation with UTI, and it is associated with increased risks of progressive renal damage. The risk of parenchymal defects probably diminishes over time.

- There is consensus that antibiotics are beneficial in children with UTI compared with no treatment, although few studies have been done to confirm this.

Shorter courses (2–4 days) of initial intravenous antibiotics seem as effective as longer courses (7–14 days) at curing infections, preventing recurrence of infection, and preventing renal parenchymal defects in children with acute pyelonephritis.

Oral antibiotics may be as effective as intravenous antibiotics at treating UTI (including pyelonephritis) and preventing complications.

Single doses or single-day courses of oral antibiotics may be less effective than longer courses of oral antibiotics at treating UTI in children.

Shorter courses (2–4 days) of oral antibiotics seem as effective as longer courses at treating UTI in children without acute pyelonephritis or known renal tract abnormalities and may be associated with fewer adverse effects.

We don't know whether immediate empirical antibiotic treatment is more effective at preventing renal parenchymal defects compared with treatment after a delay of 24 hours.

Immediate treatment may reduce the risk of renal parenchymal defects compared with treatment delayed for over 4 days.

- Prophylactic antibiotics probably don't reduce the risk of recurrent UTI, and can cause adverse effects.

  Immunotherapy, used in addition to prophylactic antibiotics, may reduce recurrence of UTI, but studies so far have been small.

- Surgical correction of moderate to severe vesicoureteric reflux may be no more effective than medical management in preventing UTI recurrence or complications and increases morbidity associated with surgery.

  Children with minor functional anomalies do not seem to develop renal parenchymal defects, and so may not benefit from surgery for minor functional anomalies.

DEFINITION

Urinary tract infection (UTI) is defined by the presence of a pure growth of more than 10^5 colony forming units of bacteria per millilitre of urine. Lower counts of bacteria may be clinically important, especially in boys, and in specimens obtained by urinary catheter. Any growth of typical urinary pathogens is considered clinically important if obtained by suprapubic aspiration. In practice, three age ranges are usually considered on the basis of differential risk and different approaches to management: children under 1 year; young children (1–4, 5, or 7 years, depending on the information source); and older children (up to 12–16 years). Recurrent UTI is defined as a further infection by a new organism. Relapsing UTI is defined as a further infection with the same organism.

INCIDENCE/ PREVALENCE

Boys are more susceptible to UTI than girls before the age of 6 months; thereafter, the incidence is substantially higher in girls than in boys. [1] Estimates of the true incidence of UTI depend on rates of diagnosis and investigation. [1] [2] Observational studies have found that UTIs have been diagnosed in Sweden in at least 2.2% of boys and 2.1% of girls by age 2 years, [1] in 7.8% of girls and 1.7% of boys by age 7 years, [3] and in the UK in 11.3% of girls and 3.6% of boys by age 16 years. [4]

AETIOLOGY/ RISK FACTORS

The normal urinary tract is sterile. Contamination by bowel flora may result in urinary infection if a virulent organism is involved, or if the child is immunosuppressed. In neonates, infection may originate from other sources. ***Escherichia coli*** accounts for about 75% of all pathogens. ***Proteus*** is more common in boys (one study found that proteus caused 33% of UTI infections in boys aged 1–16 years, compared with 0% of UTI infections in girls aged 1–16 years). [5] **Obstructive anomalies** are found in up to 4%, and **vesicoureteric reflux** in 8% to 40% of children being investigated for their first UTI. [6] One meta-analysis of 12 cohort studies (537 children admitted to hospital for UTI, 1062 kidneys) found that 36% of all kidneys had parenchymal defects on dimercaptosuccinic acid (DMSA) scintigraphy, and that 59% of children with vesicoureteric reflux on micturating cystourethrography had at least one scarred kidney (pooled positive likelihood ratio 1.96, 95% CI 1.51 to 2.54; pooled negative likelihood ratio 0.71, 95% CI 0.58 to 0.85). There was evidence of heterogeneity in likelihood ratios among studies. The authors concluded that vesicoureteric reflux is a weak predictor of renal damage in children admitted to hospital. [7] Thus, although vesicoureteric reflux is a major risk factor for adverse outcome, other factors, some of which have not yet been identified, are also important. **Family history:** Vesicoureteric reflux itself runs in families. In one review article, the incidence of reflux in siblings ranged from 26% (a cohort of asymptomatic siblings) to 86% (siblings with a history of UTI) compared with a rate of less than 1% in the general population. [8] Although some gene variants seem more common in children who suffer renal damage, no clear link has yet been established between specific genes and an adverse outcome. [9] Local or systemic immune problems are also likely to be factors in the development of UTI.

PROGNOSIS

Recurrence: A study in the UK found that 78% of girls and 71% of boys presenting with UTI within the first year of life experienced recurrence, and that 45% of girls and 39% of boys presenting after their first year of life developed further infections. [10] **Vesicoureteric reflux:** In a longitudinal study, 84% of children (572 children with UTI and vesicoureteric reflux) had spontaneous resolution during

medical follow-up at between 5 and 15 years. [11] **Renal parenchymal defects:** A systematic review of imaging in childhood UTI suggested that renal parenchymal defects (assessed with intravenous pyelogram [IVP] or dimercaptosuccinic acid [DMSA] scan) occurs in 5% to 15% of children within 1 to 2 years of their first diagnosed UTI. [6] Between 32% and 70% of these parenchymal defects were noted at the time of initial assessment, suggesting a high level of pre-existing scarring, perhaps caused by previously unrecognised infection. [6] This percentage did not substantially alter, despite an increasing referral rate, during the 3 years studied. One meta-analysis of 12 cohort studies (537 children admitted to hospital for UTI, 1062 kidneys) found that 36% of all kidneys had parenchymal defects on DMSA scintigraphy, and that 59% of children with vesicoureteric reflux on micturating cystourethrography had at least one scarred kidney (pooled positive likelihood ratio 1.96, 95% CI 1.51 to 2.54; pooled negative likelihood ratio 0.71, 95% CI 0.58 to 0.85). However, there was evidence of heterogeneity in likelihood ratios among studies. The authors concluded that vesicoureteric reflux is a weak predictor of renal damage in children admitted to hospital. [7] A retrospective population-based study in the UK suggested that 4.3% of boys and 4.7% of girls develop parenchymal defects (assessed using DMSA scans after their first referral for UTI). [4] **New or progressive renal parenchymal defects and recurrent UTI:** The systematic review reported on four studies that provided at least 2 years' follow-up: new renal parenchymal defects developed in 1.6% to 23% of children, and existing renal parenchymal defects progressed in 6% to 34%. [6] It is unclear whether figures for new parenchymal defects included any children who were previously unscarred. The highest rates of renal parenchymal defects were associated with the highest rates of recurrent UTI. [6] A further study showed that, in children aged 5 years or over, abnormal DMSA scans were noted in 64/118 (55%) children presenting with recurrent UTI, whereas 7/44 (15%) who presented with "first UTI" had renal parenchymal defects (OR for recurrences causing renal parenchymal defects 6.3, 95% CI 2.6 to 15.2). [12] However, recurrent UTI may be less important as a risk factor for renal parenchymal defects in older children. One study showed that, in children with initially normal scans at 3 or 4 years of age, 5/176 (3%) children aged 3 years at presentation, and 0/179 (0%) aged 4 years at presentation had developed renal parenchymal defects between 2 and 11 years later. [13] Of those children who developed renal parenchymal defects, 4/5 (80%) had a definite history of recurrent UTI, in all cases at least three episodes (OR for recurrences causing renal parenchymal defects 11.5, 95% CI 1.3 to 106.1). [13] Another study (287 children with severe vesicoureteric reflux treated either medically or surgically for any UTI) used serial DMSA scintigraphy to evaluate the risk of renal parenchymal defects over 5 years. It found that younger children (aged under 2 years) were at greater risk of renal parenchymal defects than older children, regardless of treatment for the infection (deterioration in DMSA scan over 5 years: 21/86 (24%) for younger children *v* 27/201 (13%) for older children; RR 1.82, 95% CI 1.09 to 3.03). [14] It is likely that children who present when older, and who are found to have renal parenchymal defects, will have had at least one previous UTI that remained undiagnosed. Many children seem to lose their susceptibility to renal damage with age. **Consequences for longer term:** One long-term follow-up study in the UK found that children with renal parenchymal defects and vesicoureteric reflux at presentation, or with just one of these followed by documented UTI, were associated with an increased risk of progressive renal damage compared with children presenting without these features (RR of progressive renal damage 17, 95% CI 2.5 to 118). [10] Persistent renal parenchymal defects may be associated with future complications, such as poor renal growth, recurrent adult pyelonephritis, impaired glomerular function, early hypertension, and end-stage renal failure. [15] [16] [17] [18] A combination of recurrent UTI, severe vesicoureteric reflux, and the presence of renal parenchymal defects at first presentation, is associated with the worst prognosis.

AIMS OF INTERVENTION

To relieve acute symptoms; to eliminate infection; and to prevent recurrence, renal damage, and long-term complications.

OUTCOMES

Short term: clinical symptoms and signs (dysuria, frequency, and fever); urine culture; incidence of new renal scars. **Long term:** incidence of recurrent infection; prevalence of renal parenchymal defects; renal size and growth; renal function; prevalence of hypertension and renal failure.

METHODS

Clinical Evidence search and appraisal July 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to July 2009, Embase 1980 to July 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 2 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing at least 20 individuals, of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies

described as "open", "open label", or not blinded, unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 20). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatment of acute urinary tract infection in children?

OPTION ANTIBIOTICS VERSUS PLACEBO

We found no direct information from RCTs about the effects of antibiotics in the treatment of children with UTI.

For GRADE evaluation of interventions for urinary tract infection in children, see table , p 20 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: Placebo-controlled trials of antibiotics in children with UTIs would be considered unethical, as there is strong consensus that antibiotics are likely to be beneficial.

Clinical guide:
The improved response seen with longer compared with very short courses of antibiotics is indirect evidence that antibiotics are likely to be more effective than no treatment.

OPTION SHORTER VERSUS LONGER COURSES OF INITIAL INTRAVENOUS ANTIBIOTICS IN CHILDREN WITH PYELONEPHRITIS

Shorter courses of initial intravenous antibiotics versus longer courses of initial intravenous antibiotics Shorter courses (2–4 days) and longer courses (7–14 days) of initial intravenous antibiotics are equally effective at curing infections in children aged 2 weeks to 16 months with acute pyelonephritis (high-quality evidence).

Recurrent infection
Shorter courses of initial intravenous antibiotics versus longer courses of initial intravenous antibiotics Shorter courses (2–4 days) and longer courses (7–14 days) of initial intravenous antibiotics seem equally effective at preventing recurrence of infections at 6–12 months in children aged 2 weeks to 16 months with acute pyelonephritis (moderate-quality evidence).

Renal parenchymal defects
Shorter courses of initial intravenous antibiotics versus longer courses of initial intravenous antibiotics Shorter courses (2–4 days) and longer courses (7–14 days) of initial intravenous antibiotics seem equally effective at preventing renal parenchymal defects at 3–6 months in children aged 2 weeks to 16 months with acute pyelonephritis (moderate-quality evidence).

For GRADE evaluation of interventions for urinary tract infection in children, see table , p 20 .

Benefits: **Longer versus shorter courses of initial intravenous (IV) antibiotics:**
We found one systematic review (search date 2006, 5 RCTs, 534 children aged 2 weeks to 16 years with acute pyelonephritis) comparing shorter regimens of IV antibiotics (2–4 days of initial IV antibiotics [ceftriaxone, temocillin, or cefotaxime] followed by oral antibiotics [cefixime, ceftibuten, amoxicillin, or amoxicillin/clavulanic acid {co-amoxiclav}] for 7–14 days) versus longer regimens of IV antibiotics (2–4 days of initial IV antibiotics [ceftriaxone, temocillin, or cefotaxime] followed by further IV antibiotics [ceftriaxone, temocillin, amikacin plus ampicillin, gentamicin plus ampicillin, or cefotaxime] for 7–14 days. [19]

One RCT included IV temocillin plus amoxicillin/clavulanic acid in the longer IV-treatment group. Two RCTs converted the longer IV-antibiotics group to oral treatment after 7–10 days to complete 15–21 days of treatment. The review found no significant difference between shorter and longer courses of IV antibiotics in persistent bacteriuria after treatment (4 RCTs, 305 children; 4/149 [3%] with shorter IV antibiotics *v* 6/156 [4%] with longer IV antibiotics; RR 0.78, 95% CI 0.24 to 2.55), and no significant difference in recurrent UTI within 6–12 months (4 RCTs, 445 children; 13/221 [6%] with shorter IV antibiotics *v* 12/224 [5%] with longer IV antibiotics; RR 1.15, 95% CI 0.52 to 2.51). The review also found no significant difference in persisting renal parenchymal defects at 3–6 months (dimercaptosuccinic acid [DMSA] scintigraphy) either in children with renal parenchymal damage on an initial DMSA scan (3 RCTs, 315 children; 63/161 [39%] with shorter IV antibiotics *v* 55/154 [36%] with longer IV antibiotics; RR 1.10, 95% CI 0.84 to 1.45) or in all children with acute pyelonephritis (3 RCTs, 343 children; 63/172 [37%] with shorter IV antibiotics *v* 55/171 [32%] with longer IV antibiotics; RR 1.13, 95% CI 0.86 to 1.49). Subgroup analyses found no significant difference in persisting renal parenchymal defects at 3–6 months between shorter and longer courses of IV antibiotics in children with or without vesicoureteric reflux (with reflux, 2 RCTs, 81 children; 17/39 [44%] with shorter IV antibiotics *v* 28/86 [33%] with longer IV antibiotics; RR 0.99, 95% CI 0.56 to 1.74; without reflux, 2 RCTs, 173 children; 34/87 [39%] with shorter IV antibiotics *v* 28/86 [33%] with longer IV antibiotics; RR 1.19, 95% CI 0.81 to 1.76). Subgroup analyses also found no significant difference in persisting renal parenchymal defects at 3–6 months between shorter and longer courses of IV antibiotics in children under 1 year of age and 1 year of age or over (age under 1 year, 1 RCT, 91 children; 11/37 [28%] with shorter IV antibiotics *v* 11/54 [20%] with longer IV antibiotics; RR 1.46, 95% CI 0.71 to 3.01; age 1 year or over, 1 RCT, 129 children; 29/73 [40%] with shorter IV antibiotics *v* 25/56 [45%] with longer IV antibiotics; RR 0.89, 95% CI 0.59 to 1.34). [19] .

Harms:

Longer versus shorter courses of initial intravenous (IV) antibiotics:
The review found no significant difference in gastrointestinal adverse effects between shorter and longer courses of IV antibiotics (2 RCTs, 175 children; 10/85 [12%] with shorter IV antibiotics *v* 8/90 [9%] with longer IV antibiotics; RR 1.29, 95% CI 0.55 to 3.05). [19]

Comment:

Studies employing follow-up DMSA scans on unselected groups of children without known risk factors for renal parenchymal defects frequently have low follow-up rates; these studies have not been included in this *Clinical Evidence* review.

The incidence of renal parenchymal defects, the most important of the outcomes measured, was similar between treatments. One RCT identified by the systematic review [19] assessed treatment costs and days spent in hospital in children receiving shorter and longer courses of IV antibiotics, and found that both outcomes were markedly increased for children receiving longer courses of IV antibiotics.

Clinical guide:
Shorter courses of IV antibiotics are of benefit both to the patient and economically compared with longer courses. It is therefore suggested that longer courses should only be used where clinical judgement indicates that a shorter course would be unwise.

OPTION ORAL ANTIBIOTICS VERSUS INITIAL INTRAVENOUS ANTIBIOTICS

Cure of infection
Oral antibiotics alone compared with intravenous (IV) followed by oral antibiotics Oral antibiotics alone seem as effective as 3 days of IV antibiotics followed by oral antibiotics at decreasing time to fever resolution and increasing the proportion of children with sterile urine after 72 hours, in children aged 1 month to 16 years with acute pyelonephritis (moderate-quality evidence).

Recurrent infection
Oral antibiotics alone compared with IV followed by oral antibiotics Oral antibiotics alone seem as effective as 3 days of IV antibiotics followed by oral antibiotics at preventing recurrent infection 6 months after an episode of acute pyelonephritis, in children aged 1 month to 16 years (high-quality evidence).

Renal parenchymal defects
Oral antibiotics alone compared with IV followed by oral antibiotics Oral antibiotics alone seem as effective as 3 days of IV antibiotics followed by oral antibiotics at improving the persistence or size of renal parenchymal defects 6–12 months after an episode of acute pyelonephritis, in children aged 1 month to 16 years (moderate-quality evidence).

For GRADE evaluation of interventions for urinary tract infection in children, see table , p 20 .

Benefits:

Oral antibiotics alone versus initial intravenous (IV) antibiotics then oral antibiotics:
We found one systematic review (search date 2006, 3 RCTs, 960 children aged 2 weeks to 16 years with acute pyelonephritis) comparing oral antibiotics (cefixime or amoxicillin/clavulanic acid [co-amoxiclav]) for 10–14 days versus IV antibiotics (cefotaxime or ceftriaxone) for 3 days or until resolution of fever, followed by oral antibiotics for 7–11 days. [19] The review meta-analysed results from multiple RCTs for three outcomes; for all other outcomes we report the results for each individual RCT below. The systematic review found no significant difference in the incidence of persistent renal parenchymal defects on dimercaptosuccinic acid (DMSA) scan at 6–12 months between oral antibiotics and initial IV antibiotics (3 RCTs, 824 children; 63/409 [15%] with oral antibiotics *v* 80/415 [19%] with initial IV antibiotics; RR 0.80, 95% CI 0.50 to 1.26). It also found no significant difference between groups in the incidence of persistent renal parenchymal defects on DMSA scan at 6–12 months in a subgroup of children with defects on the initial DMSA scan (3 RCTs, 259 children; 64/276 [23%] with oral antibiotics *v* 78/259 [30%] with initial IV antibiotics; RR 0.79, 95% CI 0.53 to 1.16). The data for one of the RCTs included in these two meta-analyses were abstract data only. The systematic review found no significant difference in time to fever resolution between oral antibiotics and initial IV antibiotics (2 RCTs, 808 children; mean difference +2.05 hours, 95% CI –0.84 hours to +4.94 hours).

The first RCT identified by the review (309 children, aged 2 years or under, fever over 38.2 °C, with a first UTI confirmed from catheter specimen) compared oral cefixime for 14 days (double dose on day 1) with a combination of initial IV cefotaxime for 3 days followed by 11 days of oral cefixime. [20] The systematic review performed a post hoc subgroup analysis of this RCT and found no significant difference in persistent renal parenchymal defects at 6 months between oral and initial IV antibiotics in children with or without vesicoureteric reflux (with reflux: 15/57 [26%] with oral antibiotics *v* 7/50 [14%] with initial IV antibiotics; RR 1.88, 95% CI 0.83 to 4.24; without reflux: 4/75 [5%] with oral antibiotics *v* 6/90 [7%] with initial IV antibiotics; RR 0.80, 95% CI 0.23 to 2.73. [19] In children with reflux grades III to IV (see table 1, p 19), a post hoc subgroup analysis found that initial IV treatment reduced the risk of renal scarring at 6 months compared with oral antibiotics; however, the results were of borderline significance (new renal scarring on DMSA scan within 6 months: 8/24 [33%] with oral treatment *v* 1/22 [5%] with initial IV treatment; RR 7.33, 95% CI 1.00 to 54.01). [19] The review found no significant difference between groups in the size of parenchymal defects on DMSA scan at up to 6 months (mean difference –0.70, 95% CI –1.74 to +0.34). It also found no significant difference between groups in reinfection rate (symptomatic reinfection rate within 6 months: 7/140 [5%] with oral treatment *v* 11/147 [7%] with initial IV treatment, RR 0.67, 95% CI 0.27 to 1.67). [19]

The second RCT identified by the review (502 children aged 1 month to under 7 years with acute pyelonephritis according to urinalysis and urine culture, and at least 2 of the following: fever 38 °C or above, inflammatory indicies in the first 48 hours, or neutrophil count above normal) compared oral amoxicillin/clavulanic acid 50 mg/kg daily for 10 days versus IV ceftriaxone 50 mg/kg daily followed by oral amoxicillin/clavulanic acid 50 mg/kg/day for 7 days. [21] The RCT reported that 52/502 (10%) children did not fulfil the inclusion criteria, but it performed an intention-to-treat analysis of children randomised. The RCT found no significant difference in the proportion of children with sterile urine 72 hours after initiation of treatment (185/186 [99%] with oral antibiotics *v* 203/204 [100%] with initial IV antibiotics; mean difference –0.05%, 95% CI –1.5% to +1.4%). The children and their parents were not blinded to treatment received, and it is unclear whether the assessors of fever and sterile urine were blinded to treatment; however, the assessors of the DMSA scans were blinded to treatment allocation. Two children in the oral antibiotics group (2/244 [1%]) had their antibiotic changed from amoxicillin/clavulanic acid because of amoxicillin/clavulanic acid resistance, and 61 children in the initial-IV group (61/258 [24%]) received IV treatment for more than 3 days, usually because of a weekend, holiday period, or change of physician. The third RCT identified by the review does not meet *Clinical Evidence* reporting criteria, as it has a follow-up rate of less than 80%, and therefore it is not reported further here.

Harms:

Oral antibiotics alone versus initial intravenous (IV) antibiotics then oral antibiotics:
The first RCT [20] identified by the systematic review [19] gave no information about adverse effects. However, it reported that 1/153 (0.7%) children in the oral group could not complete the treatment because of vomiting. The second RCT [21] identified by the systematic review [19] reported the following adverse effects, but did not assess significance: diarrhoea or vomiting (13/244 [5%] with oral antibiotics *v* 1/258 [0.4%] with initial IV antibiotics), erythema (1/244 [0.4%] with oral antibiotics *v* 1/258 [0.4%] with initial IV antibiotics), neutropenia (1/244 [0.4%] with oral antibiotics *v* 0/258 [0%] with initial IV antibiotics), and Candida (0/244 [0%] with oral antibiotics *v* 1/258 [0.4%] with initial IV antibiotics). A change of antibiotic was required because of adverse effects in 10/244 (4%) children treated with oral antibiotics versus 0/258 (0%) treated with initial IV antibiotics; significance not assessed.

Comment: The first RCT [20] identified by the review [19] excluded 3/309 (1%) children because investigators considered that the severity of symptoms in these children warranted IV treatment. [20] .

Clinical guide:
Oral antibiotics seem an effective alternative to IV treatment for most children presenting with suspected acute pyelonephritis. Few children in the RCTs identified by the systematic review [19] could not complete oral treatment because of vomiting or other adverse effects, although, in one RCT, children receiving oral antibiotics (amoxicillin/clavulanic acid) required a change in antibiotic because of adverse effects, whereas no children in the initial-IV group (ceftriaxone followed by amoxicillin/clavulanic acid) required a change of antibiotic. [21] The RCTs identified by the systematic review excluded small numbers of children with severe or recurrent symptoms, or with known urinary tract abnormality, and only included children with first UTI; these children represent a lower-risk group than children with recurrent UTI. This means that the benefits of oral antibiotics could be less (than shown here) for children in higher-risk groups. Although rates of renal parenchymal defects at 6 months were not significantly different between children with and without vesicoureteric reflux, one RCT suggested a trend towards more scarring in children with severe reflux taking oral antibiotics alone compared with initial IV followed by oral antibiotics. Additionally, in the few children with moderate or severe vesicoureteric reflux, scarring at 6 months was seen in 33% of children treated with oral antibiotics compared with 5% of children treated with initial IV followed by oral antibiotics, although this difference was not significant and the confidence intervals for this calculation were wide. [20]

OPTION SINGLE-DOSE OR SINGLE-DAY COURSES OF ORAL ANTIBIOTICS VERSUS LONGER COURSES OF ORAL ANTIBIOTICS

Cure of infection
Single-dose or single-day courses of oral antibiotics compared with longer courses of oral antibiotics Single doses or single-day courses may be less effective than longer courses (over 5–14 days) of oral antibiotics at curing infection in children with UTI (very low-quality evidence).

Recurrent infection
Single-dose or single-day courses of oral antibiotics compared with longer courses of oral antibiotics We don't know whether single doses or single-day courses are as effective as longer courses (7–14 days) of oral antibiotics at reducing recurrent infection in children with UTI (low-quality evidence).

For GRADE evaluation of interventions for urinary tract infection in children, see table , p 20 .

Benefits: **Single-dose or single-day courses of oral antibiotics versus longer courses of oral antibiotics:**
We found two systematic reviews. [22] [23] The first review (search date 1999, 22 RCTs, 1279 children aged under 18 years with culture-confirmed UTI without pyelonephritis) compared shorter (single dose, 1–4 days) versus longer (more than 5 days) courses of oral antibiotics. [22]

The second review (search date 2001, 17 RCTs, 1126 children aged under 18 years with acute but not recurrent UTI) compared shorter (3 days or less) versus longer (7–14 days) courses of oral antibiotics. [23] The two reviews had 13 RCTs in common. Both systematic reviews included poor-quality RCTs (see comment below).

The first systematic review performed a subgroup analysis of single doses versus longer courses of oral antibiotics. [22] It found no significant difference in cure rates at over 3 to under 30 days between single doses and longer courses (number of RCTs and sample size not clear; overall difference between groups in proportion of children cured +0.02%, 95% CI –1.8% to +0.21%; absolute values not reported). The review noted significant heterogeneity for this outcome (P = 0.10; significant heterogeneity defined by review as P less than 0.05), which was possibly attributable to different agents being used in the RCTs.

The second systematic review also performed subgroup analyses of single doses versus longer courses of oral antibiotics. [23] It found that single doses significantly increased treatment failure 2 weeks after cessation of treatment compared with longer courses (7 RCTs, 293 children; RR 2.73, 95% CI 1.38 to 5.40; absolute values not reported). However, the second review found no significant difference in reinfection over 2 weeks after cessation of treatment between single doses and longer courses (3 RCTs, 312 children; RR 0.37, 95% CI 0.12 to 1.18; absolute values not reported). Because of methodological concerns, the results from these two systematic reviews should be interpreted with caution (see comment below).

Harms:

Single-dose or single-day courses of oral antibiotics versus longer courses of oral antibiotics:
The first systematic review reported that dose-related adverse effects, such as neutropenia with beta-lactam antibiotics, seemed to increase in frequency with the length of administration. [22] The second systematic review gave no information about adverse events. [23]

Co-trimoxazole:
The use of trimethoprim–sulfamethoxazole (co-trimoxazole; TMP-SMX) is associated with rare but serious adverse effects such as Stevens–Johnson syndrome, and with blood disorders. Children are at lower risk than adults. In the UK, the Committee on Safety of Medicines advises that TMP-SMX should only be used where there is good evidence of bacteriological sensitivity, and reason to prefer this combination of drugs to a single antibacterial. [24] See also harms of prophylactic antibiotics, p 11 .

Comment:

The RCTs included in the reviews [22] [23] differed in the lengths of treatment and antibiotics used; the definitions of cure, relapse, and reinfection; and the diagnostic criteria for pyelonephritis or complicated UTI. Additionally, for some RCTs, the antibiotics used in the longer and shorter groups were not the same.

Clinical guide:
We found no good evidence that single-dose or single-day antibiotic treatment is a sufficiently effective treatment for UTI in children. The findings in this review suggest that, in the absence of previous positive radiology, children with only lower-UTI symptoms may receive shorter courses of antibiotics, typically a 3-day course. This mirrors the findings in adults. This rule of thumb will necessarily apply only to older children, in whom it is easier to differentiate lower and upper tract symptoms. It may be difficult to apply this to the management of first-time UTI, as risk is unknown.

OPTION SHORTER COURSES (2–4 DAYS) OF ORAL ANTIBIOTICS VERSUS LONGER COURSES OF ORAL ANTIBIOTICS

Cure of infection
Shorter courses (2–4 days) of oral antibiotics versus longer courses of oral antibiotics Shorter courses (2–4 days) of oral antibiotics and longer courses (7–14 days) seem equally effective at curing infection in children with culture-confirmed UTI, without acute pyelonephritis or known renal tract abnormalities (high-quality evidence).

Recurrent infection
Shorter courses (2–4 days) of oral antibiotics versus longer courses of oral antibiotics Shorter courses (2–4 days) of oral sulphonamides and longer courses (7–14 days) of oral sulphonamides seem to be equally effective at preventing recurrence in children with culture-confirmed UTI, without acute pyelonephritis or known renal tract abnormalities (high-quality evidence).

Adverse effects
Shorter courses of antibiotics may be associated with fewer adverse effects than longer courses.

For GRADE evaluation of interventions for urinary tract infection in children, see table , p 20 .

Benefits:

We found three systematic reviews comparing longer versus shorter courses of oral antibiotics. [22] [23] [25] The first review (search date 1999, 22 RCTs, 1279 children aged under 18 years with culture-confirmed UTI without pyelonephritis) compared shorter (single dose, 1–4 days) versus longer (more than 5 days) courses of oral antibiotics. [22]

The second review (search date 2001, 17 RCTs, 1126 children aged under 18 years with acute but not recurrent UTI) compared shorter (3 days or less) versus longer (7–14 days) courses of oral antibiotics. [23]

The third review (search date 2005, 10 RCTs, 652 children aged between 3 months and 18 years with culture-confirmed UTI, without acute pyelonephritis or known renal tract abnormalities) compared shorter (2–4 days) versus longer (7–14 days) courses of the same oral antibiotic. [25] The three systematic reviews between them included 26 RCTs; 3 RCTs were common to all three reviews, 10 RCTs were common to the first and second reviews, one RCT was common to the first and second reviews, and 6 RCTs were common to the second and third reviews. We report here only the third systematic review, [25] which reports our direct comparison of interest.

Shorter courses (2–4 days) versus longer courses of oral antibiotics:
The third systematic review compared shorter versus longer courses of the same antibiotic (amoxicillin, nitrofurantoin, trimethoprim–sulfadiazine, nalidixic acid, pivmecillinam, nitrofurantoin, amoxicillin/clavulanic acid [co-amoxiclav], or cefuroxime) and excluded antibiotic courses of less than 2 days' duration. [25] The review found no significant difference between shorter and longer

antibiotic courses in rates of UTI up to 10 days after the end of treatment (7 RCTs, 423 children; 34/232 [15%] with shorter *v* 27/191 [14%] with longer; RR 1.06, 95% CI 0.64 to 1.76). [25] It also found no significant difference between shorter and longer courses in UTI at 1–15 months after treatment (8 RCTs, 507 people: 62/267 [23%] with shorter *v* 57/240 [24%] with longer; RR 0.95, 95% CI 0.70 to 1.29). The review found no significant difference between shorter and longer courses of sulphonamides, such as trimethoprim–sulfamethoxazole (co-trimoxazole; TMP-SMX), for persistence of UTI at the end of treatment (4 RCTs, 289 children; 19/161 [12%] with shorter *v* 19/128 [15%] with longer; RR 0.80, 95% CI 0.45 to 1.41), or recurrence of UTI 1 to 15 months after treatment (5 RCTs, 327 children; 38/172 [22%] with shorter *v* 33/155 [21%] with longer; RR 0.96, 95% CI 0.64 to 1.44; see comment below). [25]

Harms:

Shorter courses (2–4 days) versus longer courses of oral antibiotics:
The third systematic review [25] found no significant difference in rates of antibiotic-resistant UTI between shorter and longer courses of antibiotics (3 RCTs, 46 children; 3/28 [11%] with shorter *v* 6/18 [33%] with longer; RR 0.39, 95% CI 0.12 to 1.29). [25]

Co-trimoxazole:
The use of trimethoprim–sulfamethoxazole (co-trimoxazole; TMP-SMX) is associated with rare but serious adverse effects such as Stevens–Johnson syndrome and blood disorders. Children are at lower risk than adults. In the UK, the Committee on Safety of Medicines advises that TMP-SMX should only be used where there is good evidence of bacteriological sensitivity, and reason to prefer this combination of drugs to a single antibacterial. [24] See also harms of prophylactic antibiotics, p 11 .

Comment:

The third systematic review included an unspecified number of children with asymptomatic bacteriuria. [25] The clinical importance of treating this group remains unclear. Several factors may reduce the generalisability of results to all children with lower UTI. First, the third review [25] excluded children with acute pyelonephritis only, which may not have excluded all cases of upper UTI. Second, all the RCTs in the third review included children with recurrent UTI, who have higher rates of treatment failure than children with no history of UTI. [25]

Clinical guide:
These findings suggest that, in the absence of previous positive radiology, children with only lower-UTI symptoms may receive shorter courses of antibiotics, typically a 3-day course. This mirrors the findings in adults. This rule will necessarily apply only to older children, in whom it is easier to differentiate lower and upper tract symptoms. It may be difficult to apply this to the management of first time UTI as risk is unknown.

OPTION IMMEDIATE EMPIRICAL VERSUS DELAYED ANTIBIOTIC TREATMENT

Renal parenchymal defects
Immediate antibiotic treatment compared with delayed antibiotics Immediate antibiotic treatment (within 24 hours of presentation) seems no more effective than treatment 24 hours after the onset of fever at reducing the risk of parenchymal defects in children under 2 years of age with UTIs (low-quality evidence).

For GRADE evaluation of interventions for urinary tract infection in children, see table , p 20 .

Benefits:

Immediate empirical versus delayed antibiotic treatment:
We found no RCTs comparing immediate empirical treatment versus treatment delayed until the results of microscopy or culture are known. We found one RCT (309 children, aged 2 years or less, fever over 38.2 °C, with a first UTI confirmed from catheter specimen) comparing oral cefixime for 14 days (double dose on day 1) with a combination of initial intravenous cefotaxime for 3 days followed by 11 days of oral cefixime. [20] Retrospective analysis of its results found no evidence that children treated 24 hours after the onset of fever with either regimen were at greater risk of renal parenchymal defects than children presenting within 24 hours (9/99 [9%] of children presenting before 24 hours *v* 19/159 [12%] of children presenting later; RR 1.3, 95% CI 0.6 to 2.7; P = 0.29). These results should be interpreted with caution as the RCT was not designed to compare immediate empirical versus delayed antibiotic treatment, and because post hoc analyses are subject to bias. See also benefits of prolonged delay in antibiotic treatment, p 10 .

Harms:

Immediate empirical versus delayed antibiotic treatment:
The RCT gave no information about adverse effects. [20]

Comment:

Clinical guide:
Direct evidence for the harmful effects of delayed treatment only comes from animal studies. See comment on prolonged delay in antibiotic treatment, p 10 .

OPTION PROLONGED DELAY IN ANTIBIOTIC TREATMENT

Renal parenchymal defects
Compared with no delay Medium- to long-term delays (4 days to 7 years) in starting antibiotic treatment may be associated with an increased risk of renal scarring (very low-quality evidence).

For GRADE evaluation of interventions for urinary tract infection in children, see table , p 20 .

Benefits: We found one systematic review (search date 1994), which identified no RCTs. [6]

Harms: We found no RCTs.

Comment: We found one systematic review (search date 1994), which included five retrospective observational studies. [6] The studies found increased rates of renal parenchymal defects in children in whom diagnosis had been delayed between 4 days (in acute UTI) to 7 years (when a child presented with chronic non-specific symptoms). [6]

Clinical guide:
Direct evidence for the harmful effects of delayed treatment only comes from animal studies. Observational studies in humans suggest that small delays may be unimportant, but that delays of 4 or more days (which might occur if treatment is delayed until the results of urine culture are known) seem harmful. [6] As none of the studies set out to test this hypothesis, these findings must be interpreted with caution.

QUESTION What are the effects of interventions to prevent recurrence of urinary tract infection in children?

OPTION IMMUNOTHERAPY

Recurrent infection
Pidotimod compared with placebo Adding pidotimod (an immunotherapeutic agent) to antibiotic treatment seems to prevent recurrence compared with adding placebo in children aged 2–8 years with recurrent UTI (moderate-quality evidence).

For GRADE evaluation of interventions for urinary tract infection in children, see table , p 20 .

Benefits:

Immunotherapy versus placebo:
We found one RCT (double-blind, 60 children aged 2–8 years with recurrent UTI) in people receiving standard antibiotic treatment, which compared adding immunotherapy (pidotimod) versus adding placebo. [26] The RCT included a further 60-day phase, using half-dose pidotimod compared with half-dose placebo. The RCT found that adding pidotimod significantly reduced relapse rates at 60 days compared with adding placebo (4/30 [13%] with added pidotimod *v* 13/30 [43%] with added placebo; P less than 0.05). [26]

Immunotherapy versus antibiotics:
We found no systematic review or RCTs that meet *Clinical Evidence* reporting criteria.

Harms:

Immunotherapy versus placebo:
In the RCT in people receiving standard antibiotic treatment comparing added immunotherapy (pidotimod) versus added placebo, the only adverse effects recorded were thought to be attributable to concomitant antibiotic treatment. [26]

Immunotherapy versus antibiotics:
We found no systematic review or RCTs that meet *Clinical Evidence* reporting criteria.

Comment:

Intravenous immunoglobulin:
We found one systematic review (search date 2007, 16 RCTs, 4986 children) comparing intravenous (IV) immunoglobulin versus placebo or no treatment for preventing infection in preterm infants, low birth-weight infants, or both. [27] The specific effect on UTI was not reported. However, the review found that IV immunoglobulin prophylaxis reduced serious infections, including UTI, in preterm and low birth-weight neonates (16 RCTs, RR for all serious infections 0.82, 95% CI 0.74 to 0.92; NNT 25, 95% CI 17 to 50). [27] The dose varied from 120 mg/kg to 1 g/kg. The number of treatments varied from one to seven. It is possible that the IV immunoglobulin preparations used in these studies did not contain the necessary antibodies to prevent infection, and that the use of preparations with known specific antibodies against common pathogens in a specific neonatal intensive-care unit might be more effective. [27] [28] The greatest benefits were found in neonatal units with

higher nosocomial infection rates. It remains unclear whether IV immunoglobulin is only justified where infection-control policies have failed to reduce the infection rate. [27] Preterm and low birthweight neonates might have greater immune deficiency than other neonates, and might be expected to gain more from treatment with immunoglobulin.

Other immunotherapeutic agents:
We found one RCT (open pilot study, 40 girls with recurrent UTI) comparing immunotherapy (an antigenic extract of *Escherichia coli*) versus antibiotics (nitrofurantoin). [29] It found no significant difference in the incidence of UTI (clinical and microbiological confirmation) between treatments during 6 months of active treatment, or during the subsequent 6 months' follow-up (during active treatment: 4/21 [19%] with immunotherapy *v* 3/17 [18%] with antibiotics; P = 0.91; during follow-up: 3/21 [14%] with antigenic extract *v* 4/17 [24%] with nitrofurantoin; P = 0.78; analysis by intention to treat). [29] The RCT found no significant difference in rates of withdrawal caused by adverse events between immunotherapy (1/22 [5%] children) and antibiotics (1/18 [6%] children). [29]

We found one non-randomised, age-matched study (10 otherwise healthy girls aged 5–11 years with recurrent UTI) comparing intramuscular injections of inactivated uropathogenic bacteria versus no treatment. It found that the girls who had received the inactivated uropathogenic bacteria had reduced frequency of subsequent UTI compared with 10 other age-matched girls with UTI who had not received the inactivated bacteria preparation. [30] This study is limited by its non-randomised design and small sample size.

We found one study (40 children aged 3–12 years with recurrent UTI caused by *E coli* and no anatomical or functional impairments of the urinary tract) comparing prophylactic antibiotics (amoxicillin with clavulanic acid [co-amoxiclav] or cephalosporins) versus prophylactic antibiotics plus an immunomodulator with *E coli* antigens for 3 months, followed up for 3 months after the end of treatment. [31] The method of randomisation was not reported. The study found that urinary secretory immunoglobulin A levels, initially low in both groups, were raised 3 months after the end of treatment with antibiotics plus immunomodulator, but not with antibiotics alone. It also found that antibiotics plus immunomodulator reduced recurrences over 6 months compared with antibiotics alone (recurrences: 2/25 [8%] with antibiotics plus immunomodulator *v* 8/13 [61%] with antibiotics alone). [31]

Clinical guide:
Immunotherapies are an interesting additional mode of preventing UTI, and their effectiveness may be similar to those of antibiotics. However, published RCTs are often relatively small and use a number of different preparations that may not be licensed widely. It is therefore unlikely that immunotherapy will replace antibiotics for preventing recurrent UTI unless larger, well-designed studies are undertaken.

OPTION PROPHYLACTIC ANTIBIOTICS

Recurrent infection
Compared with placebo or no treatment Prophylactic antibiotics given for 10 weeks to 18 months seem no more effective than placebo at preventing UTI recurrence in children aged under 18 years with acute pyelonephritis or febrile UTI, with or without primary vesicoureteric reflux (moderate-quality evidence).

Different antibiotics compared with each other Nitrofurantoin is more effective at preventing recurrence of UTI compared with trimethoprim and trimethoprim–sulfamethoxazole, but is as effective as cefixime (high-quality evidence).

Renal parenchymal defects
Compared with placebo or no treatment Prophylactic antibiotics given for 12 months are no more effective than placebo at reducing parenchymal defects in children aged 2 months to 18 years with acute pyelonephritis or febrile UTI (high-quality evidence).

Adverse effects
Nitrofurantoin has been associated with higher rates of adverse effects compared with trimethoprim, but lower rates of adverse effects compared with cefixime.

Note
We found no clinically important results from RCTs about the optimum duration of prophylactic antibiotic treatment.

For GRADE evaluation of interventions for urinary tract infection in children, see table , p 20 .

Benefits: **Prophylactic antibiotics versus placebo or no treatment:**
We found two systematic reviews (search date 2006 [32] and search date 2006) [33] and two subsequent RCTs. [34] [35] The two systematic reviews had no RCTs in common for this analysis. The

first systematic review (4 RCTs, 388 children [mostly girls] aged under 18 years at risk of UTI, with or without vesicoureteric reflux [VUR], but without a renal tract abnormality or major neurological, urological, or muscular disease) compared the effects of antibiotics (nitrofurantoin, trimethoprim–sulfamethoxazole [co-trimoxazole; TMP-SMX]) versus placebo or no treatment on the risk of recurrent UTI. [32] The review found that antibiotics reduced the risk of repeat positive urine culture compared with placebo or no treatment, but this was of borderline significance (33/235 [14%] with antibiotics *v* 64/153 [42%] with placebo or no treatment; P = 0.05; RR 0.44, 95% CI 0.19 to 1.00; NNT 3, 95% CI 2 to 25). [32] The RCTs varied in the duration of antibiotic prophylaxis (10 weeks to 12 months) and method of concealment. The results from this review should be interpreted with caution; the systematic review was thorough but the RCTs it identified were methodologically weak. [32] None of the RCTs included in the systematic review used intention-to-treat analyses. Studies with inadequate or unclear allocation concealment and/or blinding produced more favourable results.

The second systematic review (2 RCTs, 279 children) compared antimicrobial prophylaxis versus no treatment in a selected population of children with primary VUR. [33] One RCT was published in an abstract only, and therefore does not meet *Clinical Evidence* reporting criteria. The other RCT identified by the systematic review (236 children aged 3 months to 18 years with a documented episode, and findings on dimercaptosuccinic acid [DMSA] scans, of acute pyelonephritis) compared antibiotic prophylaxis (trimethoprim 1–2 mg/kg once daily, sulfamethoxazole 5–10 mg/kg once daily or nitrofurantoin 1.5 mg/kg once daily) versus no treatment for 12 months. [36] The RCT identified children with VUR by voiding cystourethrogram (VCUG) before randomisation. The RCT found no significant difference in the proportion of children with recurrence of UTI (asymptomatic, cystitis, and acute pyelonephritis) between children with or without VUR, receiving prophylaxis or no treatment (with prophylaxis: 13/55 [24%] with VUR *v* 4/45 [9%] without VUR; P = 0.633; with no treatment: 13/58 [22%] with VUR *v* 14/60 [23%] without VUR; P = 0.999). The RCT did not assess the significance of antibiotic prophylaxis versus no treatment for recurrence of UTI. The systematic review assessed children with VUR and found no significant difference between antibiotic prophylaxis and no treatment in recurrence of UTI, but it did not assess children without VUR (with VUR: 13/55 [24%] with antibiotic prophylaxis *v* 10/58 [17%] with no treatment; RR 1.37, 95% CI 0.66 to 2.87). [33] The systematic review also found no significant difference between prophylaxis and no treatment in parenchymal defects in children with VUR, but did not assess children without VUR (with VUR: 5/55 [9%] with prophylaxis *v* 2/58 [3%] with no treatment; RR 2.64, 95% CI 0.53 to 13.03). [33] The RCT did not provide details about blinding. [36]

The first subsequent RCT (225 children aged 1 month to 3 years with grade I, II, or III VUR diagnosed on radiological VCUG, performed after a first episode of febrile UTI) compared prophylaxis with TMP-SMX (sulfamethoxazole 10 mg/kg and trimethoprim 2 mg/kg) once daily versus no treatment for 18 months. [34] It found no significant difference in UTI recurrence (more than 10^5 bacteria per mL of urine) at 18 months between prophylaxis and no treatment (18/103 [17%] with prophylaxis *v* 32/122 [26%] with no treatment; P = 0.15). However, a subgroup analysis by gender found that prophylaxis significantly reduced UTI recurrence at 18 months in boys compared with no treatment, but it found no significant difference in girls (in boys: P = 0.013; in girls: P = 0.8; absolute results not reported). The blinding in this RCT is not clear; participants were not blinded to treatment received, but the RCT does not state whether assessors were blinded to treatment allocation.

The second subsequent RCT (338 children aged 2 months to 7 years with a first episode of febrile UTI, with or without primary non-severe VUR) compared TMP-SMX 15 mg/kg/day or amoxicillin/clavulanic acid (co-amoxiclav) 15 mg/kg/day versus no treatment for 12 months. [35] It found no significant difference in the proportion of children with recurrent febrile UTI at 12 months between antibiotic prophylaxis and no treatment (15/211 [7%] with prophylaxis *v* 12/127 [9%] with no treatment; risk difference +2.34%, 95% CI –3.8% to +8.4%). It also found no significant difference between the two groups in median time to febrile recurrence (113 days for both groups; absolute values for each group not reported; P = 0.36). However, the review found that antibiotic prophylaxis significantly decreased the proportion of children with positive urine culture and concomitant positive urinalysis at 12 months compared with no treatment (20/211 [9%] with antibiotic prophylaxis *v* 24/127 [19%] with no treatment; mean difference 9.4, 95% CI 1.5 to 17.3; P = 0.2). The RCT performed a subgroup analysis of children with or without VUR; it found no significant difference in the proportion of children with recurrent febrile UTI at 12 months between antibiotic prophylaxis and no treatment, in children with or without VUR (with VUR: 10/82 [12%] with antibiotic prophylaxis *v* 9/46 [20%] with no treatment; mean difference +7.5, 95% CI –6.0 to +20.1; without VUR: 5/129 [4%] with antibiotic prophylaxis *v* 3/81 [4%] with no treatment; mean difference –0.2, 95% CI –5.5 to +5.1). The RCT also found no significant difference in new parenchymal defects, and in defects at the first site of pyelonephritis on DMSA scans at 12 months, between antibiotic prophylaxis and no treatment (new parenchymal defects: 2/187 [1%] with antibiotic prophylaxis *v* 2/108 [2%] with no treatment; mean difference +0.8, 95% CI –2.1 to +3.7; defects at the first site of pyelonephritis: 48/187 [26%] with antibiotic prophylaxis *v* 31/108 [0.3%] with no treatment; mean difference +3.0, 95% CI –7.6 to +13.6). In this RCT, the treatment allocation was not blinded to participants and

their parents, but was blinded to assessors of the DMSA scans; but it is not clear whether assessors of febrile UTI or urine culture were blinded to treatment allocation. Nine children allocated to the no-treatment arm changed to the antibiotic-prophylaxis arm (9/127 [7%]), 27 children allocated to the antibiotic arm received an antibiotic other than designated at randomisation (27/211 [13%]), and nine children allocated to the antibiotic arm discontinued treatment (9/211 [4%]); reasons for changes included UTI recurrence.

Antibiotics versus immunotherapy:
See benefits of immunotherapy, p 10 .

Different antibiotics versus each other:
We found one systematic review (search date 2006, 2 RCTs) [32] and one subsequent RCT. [37] The review included one RCT (130 children aged 1–14 years; 126 girls; 4 boys) comparing nitrofurantoin versus trimethoprim. [32] The review found that nitrofurantoin significantly reduced recurrence of UTI over 6 months compared with trimethoprim (repeat positive urine culture: 10/60 [17%] with nitrofurantoin *v* 21/60 [35%] with trimethoprim; P = 0.03; RR 0.48, 95% CI 0.25 to 0.92). [32] The review included a second RCT (60 girls aged 1–11 years) comparing nitrofurantoin versus cefixime. The review found no significant difference in the reduction of UTI at 6 to 12 months between groups (repeat positive urine culture: 3/30 [10%] with nitrofurantoin *v* 2/27 [7%] with cefixime; P = 0.7; RR 1.35, 95% CI 0.24 to 7.48). [32]

One subsequent RCT (132 children aged 3 months to 12 years with a previous history of UTI) compared TMP-SMX 2 mg/kg/day versus nitrofurantoin 1–2 mg/kg/day as a single night dose for 6 months. [37] It found that nitrofurantoin significantly reduced the rate of UTI recurrence at 6 months compared with TMP-SMX (30/66 [45%] with TMP-SMX *v* 17/66 [26%] with nitrofurantoin; RR 2.4, 95% CI 1.15 to 5; P = 0.029). The RCT provided no details about blinding.

Duration of prophylaxis:
We found no systematic review or RCTs evaluating the optimum length of prophylaxis even in children with VUR. [38]

Harms:

Prophylactic antibiotics versus placebo or no treatment:
The RCTs identified by the first systematic review gave no information about adverse effects. [32] The RCT [36] identified by the second systematic review [33] reported that "there were no reported side effects associated with the use of urinary antibiotic prophylaxis". The first subsequent RCT gave no information about adverse effects. [34]

The second subsequent RCT found that more children in the prophylaxis group experienced adverse effects than children in the no-treatment group, but significance was not assessed (25/211 [12%] with antibiotic prophylaxis v 0/127 [0%] with no treatment; significance not assessed). [35] Adverse effects were mainly vomiting or gastrointestinal intolerance.

Antibiotics versus immunotherapy:
See harms of immunotherapy, p 10 .

Different antibiotics versus each other:
One RCT identified by the systematic review found that more children discontinued treatment with nitrofurantoin than with trimethoprim, because of adverse effects including nausea, vomiting, or stomach ache (RR 3.17, 95% CI 1.36 to 7.37; NNH 5, 95% CI 3 to 13). [32] However, another included RCT found that nitrofurantoin was associated with fewer adverse effects than cefixime in the first 6 months of treatment; types of adverse effect were not specified (8/31 [26%] with nitrofurantoin *v* 18/29 [62%] with cefixime; P value not reported; reported as significant). [39]

The subsequent RCT did not report on adverse effects of treatment. [37] One RCT found that, although gastrointestinal flora were affected by treatment, *Escherichia coli* (cultured from rectal swabs from 70% of children) remained sensitive to the prophylactic antibiotic TMP-SMX). [40] However, another RCT found that children who had recently received TMP-SMX for 4 weeks or greater were more likely to have resistant *E coli* isolates than those who had received no antibiotics (absolute numbers not reported; OR 23.4, 95% CI 12.0 to 47.6) [41] (see harms of longer versus shorter courses of oral antibiotics, p 8).

Duration of prophylaxis:
We found no RCTs.

Comment:

We found one systematic review assessing the efficacy of antibiotic prophylaxis to prevent UTIs and renal parenchymal damage in children; the review is written in Spanish and we are awaiting translation to assess it for inclusion in this *Clinical Evidence* review. [42]

Overall, the methodological quality of the studies identified by both systematic reviews was poor, except for one RCT (45 children aged 6 months to 14 years) identified by the first systematic review, [32] which was double-blind and had adequate allocation concealment. The review found no difference in repeat positive urine culture at 6 months between antibiotic prophylaxis and placebo (11/21 with prophylaxis *v* 13/24 with placebo; RR 0.97, 95% CI 0.56 to 1.67). [32]

Clinical guide:
The effect of prophylactic antibiotics has probably been over-estimated in the past through reliance on studies with inadequate methodology. Recent RCTs provide no support for the routine use of prophylactic antibiotics in children after their first episode of pyelonephritis, or with low to moderate grades of VUR. Boys aged under 3 years may benefit from prophylaxis, but this may reflect the differences in the underlying causes of UTIs in boys and girls. Prophylaxis to reduce future complications may be warranted in those thought to be at especially high risk by virtue of a serious presentation, confirmed renal damage, or other factors that predispose to serious recurrences. Presumably, prophylaxis needs to be continued until children are at no further risk of progressive scarring. In many cases, this may equate to the natural resolution of VUR.

OPTION SURGICAL CORRECTION FOR MINOR FUNCTIONAL ANOMALIES

We found no clinically important results from RCTs about the effects of surgical correction of minor functional abnormalities on recurrent UTI.

For GRADE evaluation of interventions for urinary tract infection in children, **see table , p 20 .**

Benefits: We found no systematic review or RCTs.

Harms: Potential harms include the usual risks of surgery.

Comment:

Clinical guide:
One small prospective observational study (271 children) suggested that children with minor functional anomalies do not develop renal parenchymal defects and therefore may not benefit from surgery. [43] Renal parenchymal defects were present in a greater proportion of children with moderate degrees of vesicoureteric reflux (VUR) than in children with minor anomalies (proportion of children with renal parenchymal defects: 8/20 [40%] with moderate degrees of VUR *v* 0/6 [0%] with minor anomalies). In the presence of major functional anomalies, the prevention of UTIs is not the prime motive of surgical intervention.

OPTION SURGICAL CORRECTION FOR MODERATE TO SEVERE VESICOURETERIC REFLUX

Recurrent infection
Compared with prophylactic antibiotics Surgical correction of moderate to severe vesicoureteric reflux is no more effective at preventing UTIs at 1 to 10 years (high-quality evidence).

Endoscopic surgery compared with prophylactic antibiotics Endoscopic surgery (sub-ureteric implantation of a co-polymer) seems no more effective at preventing UTIs (moderate-quality evidence).

Renal parenchymal defects
Compared with prophylactic antibiotics Surgical correction of moderate to severe reflux is no more effective at preventing renal parenchymal defects (high-quality evidence).

Renal function
Compared with prophylactic antibiotics Surgical correction of moderate to severe reflux seems no more effective at preventing renal failure at 5 years (moderate-quality evidence).

Adverse effects
Surgery is associated with postoperative urinary obstruction, which can result in renal parenchymal defects.

For GRADE evaluation of interventions for urinary tract infection in children, **see table , p 20 .**

Benefits:

Surgical correction versus medical management:
We found two systematic reviews (search date 2003 [44] and 2006) [33] comparing surgical correction plus subsequent antibiotic treatment (for 1–24 months; most commonly 6 months) versus medical management (continuous prophylactic antibiotics: trimethoprim–sulfamethoxazole [co-trimoxazole; TMP-SMX], trimethoprim, or nitrofurantoin for 1–5 years) in children with moderate to severe [see table 1, p 19] vesicoureteric reflux [VUR]). The systematic reviews analysed the same RCTs relevant to this option, and we report here the results from the most recent systematic review only. [33]

Recurrent UTI:
The review found no significant difference between surgical and medical management in all UTI at 1 to 2 years and 4 to 5 years (1–2 years: 4 RCTs, 341 children; 36/177 [20%] with surgery *v* 33/164 [20%] with medical management; RR 1.07, 95% CI 0.55 to 2.09; 4–5 years: 3 RCTs, 470 children; 86/235 [37%] with surgery *v* 90/244 [37%] with medical management; RR 0.99, 95% CI 0.79 to 1.26). [33] It also found no significant difference between surgical and medical management in symptomatic UTI infections at 4 to 5 years, at 5 to 10 years, and at 10 years (4–5 years: 1 RCT, 297 children; 43/147 [29%] with surgery *v* 46/150 [31%] with medical management; RR 0.95, 95% CI 0.67 to 1.35; 5–10 years: 1 RCT, 252 children; 24/125 [19%] with surgery *v* 31/127 [24%] with medical management; RR 0.79, 95% CI 0.49 to 1.26; 10 years: 1 RCT, 252 children; 50/125 [40%] with surgery *v* 48/127 [38%] with medical management; RR 1.06, 95% CI 0.78 to 1.44). However, the review found that surgery significantly decreased the proportion of children with febrile UTI at 5 years, at 5 to 10 years, and at 10 years (5 years: 2 RCTs, 429 children; 20/211 [9%] with surgery *v* 48/218 [22%] with medical management; RR 0.43, 95% CI 0.27 to 0.70; 5–10 years: 1 RCT, 252 children; 6/125 [5%] with surgery *v* 18/127 [14%] with medical management; RR 0.34, 95% CI 0.14 to 0.82; 10 years: 1 RCT, 252 children; 17/125 [14%] with surgery *v* 32/127 [25%] with medical management; RR 0.54, 95% CI 0.32 to 0.92).

Vesicoureteric reflux:
Five RCTs in the systematic review assessed resolution of VUR; however, the review did not perform a meta-analysis because of differences in reporting (patients *v* ureters), not all patients having follow-up, and missing data. [33] The review found that surgery was more effective at abolishing reflux at 4 to 5 years compared with medical management (absence of reflux: 4 RCTs; 93–99% after surgical correction *v* 16–49% spontaneous resolution during 4–5 years of medical management; significance not assessed).

One RCT included follow-up of 102 children who had grade III/IV (dilating) reflux at entry. It found that the proportion of children who still had dilating reflux at 5 years was 57/102 (56%), and at 10 years was 27/102 (26%). A further 27/102 (26%) of children had VUR without dilation at 10 years. [45] Absence of VUR in 48/102 (47%) children at 10 years was significantly associated with less severe reflux, having grade III rather than grade IV reflux (P = 0.007), having unilateral rather than bilateral reflux (P = 0.0002), and being aged 5 years or over rather than under 5 years at study entry (P = 0.001); further data not reported. [45]

New renal parenchymal defects:
The review found no significant difference between surgery and medical management in new and progressive renal parenchymal defects at 4 to 5 years, assessed using intravenous pyelogram (IVP) scans (new and progressive renal parenchymal defects: 3 RCTs, 468 children; 97/224 [43%] with surgical correction *v* 101/244 [41%] with 4–5 years of medical management; RR 1.05, 95% CI 0.85 to 1.29). [33] Results were similar when the data were examined according to the total number of kidneys, rather than by individuals, and results were similar in two studies that assessed differences using dimercaptosuccinic acid (DMSA) scans. One RCT (306 children aged under 11 years at entry, with grades III–V [see table 1, p 19] vesicoureteric reflux [VUR], glomerular filtration rate [GFR] 70 mL/minute/1.73 m^2 or greater) [46] included in the review found only two cases of new renal parenchymal defects (one in each group) between 5 and 10 years' follow-up (1/149 [0.67%] with surgery *v* 1/153 [0.65%] with medical treatment; significance not reported). [46]

In children with more severe disease:
One RCT [47] identified by the systematic review [33] compared corrective surgery versus medical management (as above) over 4 years in children with more severe disease (25 boys and 27 girls aged 1–12 years with bilateral VUR [grades III–V] and bilateral nephropathy, GFR 20 mL/minute/1.73 m^2 or greater [more commonly children with rates of 20–70 mL/minute/1.73 m^2 are excluded]). [47] The RCT found no significant difference in the development of new renal parenchymal defects between surgical and medical management (new renal parenchymal defects: 8/50 [16%] kidneys with corrective surgery *v* 7/54 [13%] kidneys with medical treatment; RR 1.20, 95% CI 0.47 to 3.40). [47] The RCT also found that, over a period of 4 years, 20/54 (37%) kidneys of children in the medical group had spontaneous resolution to no or minimal VUR (grades 0 or I), and that corrective surgery was possible without complications in 47/50 (94%) kidneys in the surgical group (ARI 57%, 95% CI 47% to 69%). [47] The RCT found a steady decline in GFR over 10 years in children receiving medical management compared with surgery, but the difference was not significant (see table 2, p 19). [47] This RCT was too small to detect a clinically important effect of surgery in children with bilateral nephropathy.

Renal function:
The review found no significant difference between surgery and medical management in end-stage renal failure at 5 years (2 RCTs, 154 children; 3/75 [4%] with surgery *v* 3/79 [4%] with medical management; RR 1.07, 95% CI 0.23 to 5.04). [33] One RCT found that there remained no differences

in renal function at entry to the study or after 10 years, between those allocated to medical and surgical treatment. [45]

Hypertension:
The review found no significant difference between surgery and medical management in hypertension at 5 and 10 years (5 years: 2 RCTs, 154 children; 5/75 [7%] with surgery *v* 6/79 [8%] with medical management; RR 0.93, 95% CI 0.25 to 3.42; 10 years: 1 RCT, 252 children; 0/125 [0%] with surgery *v* 3/127 [2%] with medical management; RR 0.15, 95% CI 0.01 to 2.78). [33]

Endoscopic surgical management (sub-ureteric implantation of inert or hypo-allergenic substances) versus medical management:
The systematic review [33] identified one RCT (61 children aged 1 year or over) [48] that compared endoscopic techniques (sub-ureteric implantation of a co-polymer plus antibiotics) versus medical management (continuous antibiotic prophylaxis). The review found that surgery did not significantly reduce risk of UTI compared with antibiotics over 1 year; however, the RCT was probably too small to detect a significant difference (UTI over 12 months: 6/39 [15%] with endoscopic technique *v* 0/21 [0%] with medical management; significance not assessed). [33] The RCT found that endoscopic surgical management significantly improved resolution of VUR compared with medical management (proportion of people with resolution of reflux: 27/39 [69%] with endoscopic management *v* 8/21 [38%] with medical management; P = 0.029). [48]

Harms:

Surgical correction versus medical management:
The systematic review found that adverse effects were not well reported in the identified RCTs. [33] Risks with surgery may include those of any operative procedure under general anaesthetic, as well as specific postoperative complications.

Endoscopic surgical management (sub-ureteric implantation of inert or hypo-allergenic substances) versus medical management:
No adverse effects were attributed to study treatment in either the endoscopic surgery or medical management group. [48]

Postoperative obstruction of urinary tract:
Two RCTs (reported in 3 publications) reported rates of postoperative obstruction of the urinary tract. [49] [50] [51] The European arm of a multinational RCT found postoperative urinary tract obstruction in 10/151 (7%) children, with an increased risk of severe renal parenchymal defects after obstruction (RR 23.83, 95% CI 5.05 to 112.42). [49] The RCT did not report on the clinical consequences of these radiological findings. The US arm of the same multinational RCT found that 7/9 (78%) children who had postoperative obstruction developed evidence of renal parenchymal defects on DMSA scintigraphy. [50] The second RCT found that none (0/70) of the children who had surgery developed postoperative pelvi-calyceal obstruction. [51] Risks of medical management may include adverse effects of antibiotic treatment and antibiotic resistance.

Comment:

We found one systematic review assessing the efficacy of medical and surgical treatment for VUR for preventing UTIs in children, which is written in Spanish; we are awaiting translation of the paper to assess it for inclusion in this *Clinical Evidence* review. [52]

Surgery is usually considered only in children with more severe VUR (see table 1, p 19), who are less likely to experience spontaneous resolution. [53] [54] It has been suggested that the best results are obtained by centres handling the greatest number of children. [55] We found one prospective cohort study (226 children aged 5 days to 12 years who presented with UTI and VUR [grades III–IV]) with follow-up of 10 to 41 years. [15] It found that surgery increased resolution of reflux compared with medical treatment (resolution from age 8–14 years on micturating cystourethrography: 29/33 [88%] with surgery *v* 134/193 [69%] with medical treatment; ARI 19%, 95% CI 6% to 31%). The study did not compare clinical outcomes.

Clinical guide:
Surgery does not seem to provide any overall benefits compared with medical management. In addition, surgery itself can cause harm to some children, outweighing any real benefits it may have. It is unclear whether surgery has a role for the few children at highest risk of severe renal damage. As the number of such children is small, it may be difficult to prove benefit. In addition, it is unclear whether children who might benefit could be identified at an early stage, when such intervention is most likely to be beneficial.

GLOSSARY

Intravenous immunoglobulins Immunoglobulin preparations derived from donated human plasma containing antibodies prevalent in the general population.

Nosocomial infection Definitions vary but typically an infection arising at least 48–72 hours after admission to hospital. The infection may have been acquired from other people, hospital staff, the hospital environment, or from pre-existing subclinical infection.

Pyelonephritis Inflammation of the kidney and its pelvis caused by bacterial infection.

Dimercaptosuccinic acid (DMSA) scintigraphy A scan following intravenous injection of a radioisotope solution, which is excreted by the kidneys. The scan yields information about the structure and function of the urinary tract.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence 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.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Oral antibiotics versus initial intravenous (IV) antibiotics One systematic review added (search date 2006), [19] which compared oral antibiotics alone for 10–14 days versus IV antibiotics for 3 days or until resolution of fever, followed by oral antibiotics for 7–11 days in children aged 2 weeks to 16 years with acute pyelonephritis. It found no significant difference in fever resolution at 72 hours, reinfection rate at 6 months, and renal parenchymal defects at 6–12 months, between oral antibiotics and initial IV antibiotics. It also found no significant difference between groups in the incidence of persistent renal parenchymal defects on dimercaptosuccinic acid (DMSA) scan at 6–12 months in a subgroup of children with defects on the initial DMSA scan. Categorisation unchanged (Likely to be beneficial).

Shorter courses (2–4 days) of oral antibiotics versus longer courses of oral antibiotics One systematic review updated (search date 2005), [25] which compared shorter versus longer courses of the same antibiotic. It found no additional RCTs to those previously reported in this *Clinical Evidence* review. Categorisation unchanged (Likely to be beneficial).

Shorter versus longer courses of initial intravenous antibiotics in children with pyelonephritis One systematic review updated (search date 2006), [19] which compared shorter regimens of intravenous antibiotics (2–4 days followed by oral antibiotics for 7–14 days) versus longer regimens of intravenous antibiotics (2–4 days followed by further intravenous antibiotics for 7–14 days) in children aged 2 weeks to 16 years with acute pyelonephritis. It found no significant difference in persistent bacteriuria after treatment, recurrent UTI at 6–12 months, and persisting renal parenchymal defects at 3–6 months, between shorter and longer courses of intravenous antibiotics. Categorisation unchanged (shorter courses are "Likely to be beneficial").

Surgical correction for moderate to severe vesicoureteric reflux One systematic review added (search date 2006), [33] which compared surgical correction plus subsequent antibiotic treatment versus medical management (continuous prophylactic antibiotics) in children with moderate to severe vesicoureteric reflux. The review found no significant difference in recurrent infection, new and progressive parenchymal defects, and end-stage renal failure between surgical and medical management. However, the review found that surgical management was more effective than medical management at abolishing reflux. Categorisation unchanged (Unlikely to be beneficial) owing to surgical risks.

Prophylactic antibiotics One systematic review (search date 2006) [33] and two subsequent RCTs [34] [35] added, which compared antibiotic prophylaxis versus no treatment. The systematic review [33] included children with primary vesicoureteric reflux (VUR), and identified one RCT; [36] the first subsequent RCT [34] included children with febrile UTI and primary VUR; and the second subsequent RCT [35] included children with a febrile UTI, with or without VUR. The systematic review and subsequent RCTs found no significant differences in the recurrence of febrile UTI and parenchymal defects between antibiotic prophylaxis and no treatment. One further RCT added, [37] which compared trimethoprim–sulfamethoxazole versus nitrofurantoin in children with a previous history of UTI. It found that nitrofurantoin reduced the rate of UTI recurrence at 6 months compared with trimethoprim–sulfamethoxazole. Categorisation changed from "Likely to be beneficial" to "Unlikely to be beneficial".

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TABLE 1 **Severity of vesicoureteric reflux.**

Grade I	Reflux into ureters only
Grade II	Reflux into ureters, pelvis, and calyces
Grade III	Mild to moderate dilatation or tortuosity of ureters and mild to moderate dilatation of pelvis, but little or no forniceal blunting
Grade IV	As grade III, but with complete obliteration of forniceal angles, yet maintenance of papillary impressions in calyces
Grade V	Gross dilatation of ureters, pelvis, and calyces, and papillary impressions in calyces obliterated

TABLE 2 **Average glomerular filtration rates in children with bilateral vesicoureteric reflux and bilateral nephropathy at the commencement of the study, at 4 years, and at 10 years after randomisation to medical or surgical management.** [47]

Mean GFR (mL/minute)	At entry	At 4 years	At 10 years
Medical management	72.4	70.2	68.3
Surgical management	71.7	73.7	74.1
Difference in change in GFR from entry (95% CI)	–	+7.1% (–6.4% to +20.6%)	+8.9% (–10.3% to +28.2%)

GFR, glomerular filtration rate.

TABLE **GRADE evaluation of interventions for UTI in children**

Important outcomes		Cure rate (signs of infection), renal parenchymal defects, recurrent infection, renal function, adverse effects						
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatment of acute urinary tract infection in children?									
At least 7 RCTs (at least 293 children) [22] [23]	Cure rate (signs of infection)	Single-dose or single-day course of oral antibiotics *v* longer course of oral antibiotics	4	–2	–1	0	0	Very low	Quality points deducted for incomplete reporting of results and weak methods. Consistency point deducted for statistical heterogeneity
3 (312) [23]	Recurrent infection	Single-dose or single-day course of oral antibiotics *v* longer course of oral antibiotics	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and weak methods
2 (808) [19]	Cure rate (signs of infection)	Oral antibiotics alone *v* IV plus oral antibiotics	4	–1	0	0	0	Moderate	Quality point deducted for weak methods in the RCTs
1 (287) [20]	Recurrent infection	Oral antibiotics alone *v* IV plus oral antibiotics	4	0	0	0	0	High	
3 (824) [19]	Renal parenchymal defects	Oral antibiotics alone *v* IV plus oral antibiotics	4	–1	0	0	0	Moderate	Quality point deducted for weak methods in the RCTs
1 (258) [20]	Renal parenchymal defects	Immediate empirical antibiotics *v* delayed antibiotics	4	0	0	–1	0	Moderate	Directness point deducted as RCT not designed to answer this question
At least 8 RCTs (at least 507 children) [25]	Cure rate (signs of infection)	Shorter course (2–4 days) of oral antibiotics *v* longer course of oral antibiotics	4	0	0	0	0	High	
5 (327) [25]	Recurrent infection	Shorter course (2–4 days) of oral antibiotics *v* longer course of oral antibiotics	4	0	0	0	0	High	
4 (305) [19]	Cure rate (signs of infection)	Shorter course of initial IV antibiotics *v* longer course of initial IV antibiotics	4	0	0	0	0	High	
4 (445) [19]	Recurrent infection	Shorter course of initial IV antibiotics *v* longer course of initial IV antibiotics	4	0	0	0	0	High	
3 (343) [19]	Renal parenchymal defects	Shorter course of initial IV antibiotics *v* longer course of initial IV antibiotics	4	0	0	0	0	High	
5 studies [6]	Renal parenchymal defects	Prolonged delay in starting antibiotics	2	0	0	–1	0	Very low	Directness point deducted for studies not being designed to answer the question
What are the effects of interventions to prevent recurrence of urinary tract infection in children?									
1 (60) [26]	Recurrent infection	Immunotherapy *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
7 (1169) [32] [33] [34] [35]	Recurrent infection	Prophylactic antibiotics *v* placebo/no treatment	4	0	0	–1	0	Moderate	Directness point deducted for different durations of antibiotic prophylaxis

Important outcomes		Cure rate (signs of infection), renal parenchymal defects, recurrent infection, renal function, adverse effects							
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
2 (408) [33] [35]	Renal parenchymal defects	Prophylactic antibiotics *v* placebo/no treatment	4	0	0	0	0	High	
3 (309) [32] [37]	Recurrent infection	Different antibiotics versus each other	4	0	0	0	0	High	
At least 4 RCTs (at least 470 children) [33]	Recurrent infection	Surgical correction plus antibiotics *v* antibiotics alone (children with moderate/severe vesicoureteric reflux)	4	0	0	0	0	High	
3 (468) [33]	Renal parenchymal defects	Surgical correction plus antibiotics *v* antibiotics alone (children with moderate/severe vesicoureteric reflux)	4	0	0	0	0	High	
2 (154) [33]	Renal function	Surgical correction plus antibiotics *v* antibiotics alone (children with moderate/severe vesicoureteric reflux)	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (60) [33] [48]	Recurrent infection	Endoscopic surgical management *v* prophylactic antibiotics	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies. Directness: generalisability of population or outcomes. IV, intravenous