ClinicalEvidence

Urinary tract infection in children: recurrent infections

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ABSTRACT

INTRODUCTION: Up to 11% of girls and 7% of boys will have had a urinary tract infection (UTI) by the age of 16 years, and recurrence of infection is common. Vesicoureteric reflux (VUR) 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 prophylactic antibiotics to prevent recurrent urinary tract infection in children? We searched: Medline, Embase, The Cochrane Library, and other important databases up to December 2013 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). RESULTS: We found three 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 intervention: prophylactic antibiotics.

QUESTIONS

What are the effects of prophylactic antibiotics to prevent recurrent urinary tract infection in children?. 4

INTERVENTIONS

PREVENTION OF RECURRENCE

Trade off between benefits and harms

Prophylactic antibiotics (compared to placebo or no treatment, may reduce UTI incidence and weak evidence may reduce scarring in children with VUR; however, antibiotics associated with resistance and other adverse effects) 4

Unknown effectiveness

Different durations of prophylactic antibiotics New . . 7

Key points

- Up to 11% of girls and 7% of boys will have had a UTI by the age of 16 years. Recurrent UTI is common
- Vesicoureteric reflux (VUR) 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.
- Prophylactic antibiotics may be more effective than placebo at reducing the risk of recurrent UTI; however, they may increase microbial resistance to the prophylactic drug.

  Recent, well-conducted RCTs suggest a limited benefit of prophylaxis.
- Prophylactic antibiotics may be more effective than placebo at reducing renal parenchymal scarring in children with VUR.
- We found no systematic review or RCT evidence comparing different durations of antibiotics.
- Nitrofurantoin appears to be more effective than other prophylactic antibiotics, but this is balanced by the increased risk of side-effects and treatment drop-out.

Clinical context

GENERAL BACKGROUND

Prophylactic antibiotics are likely to reduce symptomatic UTI in all children and renal parenchymal defects in children with vesicoureteric reflux (VUR). However, the effect is small, the ideal duration of treatment unclear, and the possibility of differential benefit among sub-cohorts of children not investigated. Of the suitable antibiotics, nitrofurantoin causes the least microbial resistance, but the most side-effects.

FOCUS OF THE REVIEW

This systematic overview concentrates on the use of prophylactic antibiotics to prevent UTI and renal parenchymal defects in children with or without vesicoureteric reflux (VUR). This has been an area of professional debate. New evidence has emerged since our last review, modifying the conclusions of previous *BMJ Clinical Evidence* summaries.

COMMENTS ON EVIDENCE

Two updated systematic reviews have significantly added to our knowledge since our last review. They include several recently published studies, and one of these is especially large and of high quality. These have led to a subtle change in the evidence.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, July 2009, to December 2013. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the review, please see the Methods section. Searching of electronic databases retrieved 284 studies. After deduplication and removal of conference abstracts, 175 records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of 142 studies and the further review of 33 full publications. Of the 33 full articles evaluated, two systematic reviews and one RCT were included at this update.

DEFINITION

The presence of a pure growth of at least 10^7 colony-forming units of bacteria per litre of urine indicates a diagnosis of urinary tract infection (UTI). 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. Different presentation and differential risk have often led to the stratification of children by age for clinical management and research. NICE guidance defines three age groups: under 3 months; 3 months to 3 years; and over 3 years. [1] Other publications have defined risk groups as children aged up to 1 year, up to 7 years, and 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. [2] Estimates of the true incidence of UTI depend on rates of diagnosis and investigation. [2] [3] Observational studies have found that UTIs have been diagnosed in Sweden in at least 2% of boys and girls by the age of 2 years, [2] in 8% of girls and 2% of boys by age 7 years, [4] and in the UK in 11% of girls and 7% of boys by age 16 years. [5]

AETIOLOGY/ RISK FACTORS

The normal urinary tract is sterile. Contamination by bowel flora may result in urinary infection if a virulent organism is involved. 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 of the same age). [6] In a study of children presenting with acute pyelonephritis, UTIs caused by non-*E coli* organisms were more likely to be associated with permanent renal damage than *E coli* (83% *v* 57%). [7] **Obstructive anomalies** are found in up to 4%, and **vesicoureteric reflux (VUR)** in 8% to 40% of children being investigated for their first UTI. [8] 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 VUR 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 VUR is a weak predictor of renal damage in children admitted to hospital. [9] Thus, although VUR is a major risk factor for adverse outcome, other factors, some of which have not yet been identified, are also important. **Family history** VUR itself runs in families. The mode of inheritance is autosomal dominance with variable penetrance and expressivity. [10] In one review, the incidence of reflux in siblings ranged from 26% (a cohort of asymptomatic siblings) to 86% (siblings with a history of UTI). [11] In another review, 32% of siblings had VUR, but only 2% was of a severe grade (Grade III and above). [12] The rate in the general population has been calculated at 1% to 3%. [13] 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. [14] Local or systemic immune problems are also likely to be factors in the development of UTI.

PROGNOSIS

Recurrence A UK study 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. [15] **VUR** In a longitudinal study, 84% of children (572 children with UTI and VUR) had spontaneous resolution during medical follow-up at between 5 and 15 years. [16] **Renal parenchymal defects** A systematic review of imaging in childhood UTI suggested that renal parenchymal defects (assessed with intravenous pyelogram [IVP] or DMSA scan) occurs in 5% to 15% of children within 1 to 2 years of their first diagnosed UTI. [8] 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. [8] This percentage did not substantially alter, despite an increasing referral rate, during the 3 years studied. A retrospective population-based study in the UK suggested that 4.3% of boys and 4.7% of girls develop parenchymal defects (2842 children assessed using DMSA scans after their first referral

for UTI). [5] **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 2% to 23% of children, and existing renal parenchymal defects progressed in 6% to 34%. [8] 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. [8] A further study showed that, in children aged 5 years or older, 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). [17] 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. [18] 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). [18] Another study (287 children with severe VUR 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 <2 years) were at greater risk of renal parenchymal defects than older children, regardless of treatment for the infection (deterioration in DMSA scan >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). [19] 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). [15] 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. [20] [21] [22] [23] 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 prevent recurrence, renal damage, and long-term complications.
OUTCOMES	**Recurrent infection**; **renal parenchymal defects**; and **adverse effects**.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal December 2013. Databases used to identify studies for this systematic review included: Medline 1966 to December 2013, Embase 1980 to December 2013, The Cochrane Database of Systematic Reviews 2013, issue 11 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this review were systematic reviews and RCTs published in English, at least single-blinded, and containing 20 or more individuals (10 in each arm), 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. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed a priori with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the review. In addition, information that did not meet our predefined criteria for inclusion in the benefits and harms section, may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we

cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Data and quality** 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). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue which may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see Table 2, p 9). 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.bmj.com).

QUESTION What are the effects of prophylactic antibiotics to prevent recurrent urinary tract infection in children?

OPTION PROPHYLACTIC ANTIBIOTICS

Recurrent infection

Prophylactic antibiotics compared with placebo or no treatment Prophylactic antibiotics given for 10 weeks to 24 months may be more effective than placebo at preventing symptomatic UTI recurrence in children aged under 18 years, with or without primary vesicoureteric reflux (VUR); however, the results vary with the analysis used (moderate-quality evidence).

Renal parenchymal defects

Prophylactic antibiotics compared with placebo or no treatment Prophylactic antibiotics given for 1 to 3 years are more effective than placebo at reducing parenchymal defects (new or progressive damage on DMSA scan) in children with vesicoureteric reflux. However, when these two outcomes were assessed separately there was no significant difference (low-quality evidence).

Adverse effects

Prophylactic antibiotics compared with placebo or no treatment There was no difference between groups for adverse effects with prophylaxis compared to placebo or no treatment. Adverse effects were mostly minor. Prophylactic antibiotics increase microbial resistance, and many breakthrough UTIs are caused by resistant organisms. Nitrofurantoin is less liable to cause resistance, which may account for its superior effectivensss; unfortunately, this is balanced by more adverse effects and treatment drop outs.

Benefits:

Prophylactic antibiotics versus placebo or no treatment:

We found two systematic reviews (search date 2010; [24] and 2010 [25]). The first systematic review included studies if the majority of children (>50%) did not have a predisposing cause, such as a renal tract abnormality, or a major neurological, urological, or muscular disease. It identified six RCTs (1069 children) comparing prophylactic antibiotics with placebo or with no treatment. [24] Five RCTs (3 versus placebo and 2 versus no treatment) were included in the meta-analyses; the sixth RCT was a small crossover study (n = 18) that did not meet *BMJ Clinical Evidence* inclusion criteria and is, therefore, not reported further here. The second systematic review was only in children with primary VUR. [25] It found eight RCTs (1039 children), six comparing antibiotic prophylaxis with no treatment and two versus placebo. The systematic reviews had two RCTs in common, although the second systematic review only reported the subgroup analyses for children with VUR.

In the first systematic review, the duration of antibiotic prophylaxis varied from 10 weeks to 12 months and the percentage of children with VUR ranged from 0% to 42%. [24] When all five RCTs were meta-analysed, antibiotics did not appear to reduce the risk of symptomatic UTI compared to placebo/no treatment (4 RCTs,1024 children, 58/553 [10%] with antibiotics *v* 81/471 [17%] with placebo/no treatment; RR 0.75, 95% CI 0.36 to 1.53, P = 0.43; significant heterogeneity, I^2 = 62%, P = 0.05). The effect was similar in children with VUR (2 RCTs, 371 children, 24/204 [12%] with antibiotics *v* 30/167 [18%] with placebo/no treatment, RR 0.65, 95% CI 0.39 to 1.07, P = 0.088) compared to those without VUR (3 RCTs, 491 children, 20/273 [7%] with antibiotics *v* 30/218 [14%] with placebo/no treatment, RR 0.56, 95% CI 0.15 to 2.12, P = 0.40; heterogeneity, I^2 = 62%, P = 0.07). However, when the systematic review evaluated the effects of antibiotics in the two largest and most recent studies, [26] [27] there was a statistically significant reduction in the risk of symptomatic UTI (2 RCTs, 914 children, 51/499 [10%] with antibiotics *v* 67/415 [16%] with placebo/no

treatment, RR 0.68, 95% CI 0.48 to 0.95, P = 0.024). Both of these studies gave antibiotics for 12 months.

In the second systematic review, the duration of antibiotic prophylaxis varied from 1 to 3 years. [25] Antibiotic prophylaxis compared to no treatment/placebo did not significantly reduce repeat symptomatic UTI (5 RCTs, 846 children, 54/431 [13%] with prophylaxis *v* 78/415 [19%] with no treatment, RR 0.68, 95% CI 0.39 to 1.17, P = 0.16; significant heterogeneity, I^2 = 57%, P = 0.05); or febrile UTI (6 RCTs, 946 children, 68/481 [14%] with prophylaxis *v* 86/465 [18%] with no treatment, RR 0.77, 95% CI 0.47 to 1.24, P = 0.28; significant heterogeneity, I^2 = 58%, P = 0.04) at 1 to 2 years. At 1 to 3 years, antibiotic prophylaxis reduced the risk of the combined outcome of new or progressive renal damage on DMSA scan (3 RCTs, 446 children, 7/227 [3%] with prophylaxis *v* 20/219 [9%] with no treatment, RR 0.35, 95% CI 0.15 to 0.80, P = 0.014). However, there was no significant difference in either of these outcomes alone (new renal abnormality RR 0.27, 95% CI 0.06 to 1.23, P = 0.089; deterioration of existing abnormality RR 0.68, 95% CI 0.27 to 1.73, P = 0.42). There was also no significant difference in resolution of VUR after 1 to 2 years (3 RCTs, 262 children, RR 1.46, 95% CI 0.71 to 2.99, P = 0.30).

Harms:

Prophylactic antibiotics versus placebo or no treatment:
The first systematic review found two studies that reported adverse events and found no difference between antibiotics and placebo/no treatment (2 RCTs, 914 children, 19/499 [4%] with antibiotics *v* 10/415 [2%] with placebo/no treatment, RR 2.31, 95% CI 0.03 to 170.67, P = 0.70; significant heterogeneity, I^2 = 88%, P = 0.004). [24] One RCT in the analysis was unblinded and reported no adverse events in the no treatment group. The other RCT, which was blinded, found more adverse events in the placebo than in the prophylactic antibiotic group. For microbial resistance the systematic review analysed two studies, [26] [27] which reported this for a subgroup of children with repeat symptomatic UTI. There was no significant difference in the risk of microbial resistance to prophylactic drug; however, this was based on a small number of children and, therefore, may have been underpowered to show an effect (2 RCTs, 128 children, 18/51 [35%] with prophylaxis *v* 11/67 [16%] with no treatment, RR 2.40, 95% CI 0.62 to 9.26, P = 0.21). [24] Of note, while there was no significant heterogeneity in the meta-analysis (I^2 = 49%, P = 0.16); in the active treatment arms, the percentage of UTIs that were resistant organisms ranged from 28% in one study [26] to 53% [27] in the other. [24]

In the second systematic review, one study had "no reported side effects associated with the use of urinary antibiotic prophylaxis" and another study (one of the two mentioned above) reported that two participants developed thrush while on antibiotics and five developed a rash while on placebo. No significant differences were found between the groups for adverse events (2 RCTs, 356 children, 2/177 [1%] with prophylaxis *v* 5/179 [3%] with no treatment, RR 0.40 95% CI 0.08 to 2.01, P = 0.26). Risk of microbial resistance to prophylactic drug significantly increased in the prophylactic antibiotic group (4 RCTs, 134 children, 44/54 [81%] with prophylaxis *v* 19/78 [24%] with no treatment, RR 2.94 95% CI 1.39 to 6.25, P = 0.005; significant heterogeneity, I^2 = 60%, P = 0.06). [25]

Comment:

Overall, the methodological quality of the studies identified by both systematic reviews was poor. Only three RCTs were double-blinded and had adequate allocation concealment: one RCT (576 children aged 0–18 years) only met the inclusion criteria for the first systematic review, and the final RCT (46 children aged <3 months with isolated VUR) was included only in the second systematic review. [25] For four out of eight studies in the second systematic review, the authors had access to supplementary unpublished data. [25]

Three of the five studies in the first systematic review were conducted in the 1970s. The populations in these early studies were almost all girls with previous frequent UTI and normal renal tract. The two more recent studies had a more balanced gender ratio and, accordingly, the proportion with VUR increased to around 30% to 40%. [24] Overall, girls also outnumbered boys in the second systematic review, with a maximum reported ratio of 4:1 in one RCT. In one RCT (225 children aged 1 month to 3 years with grade I, II, or III VUR diagnosed on radiological voiding cystourethrogram (VCUG), performed after a first episode of febrile UTI) reporting on sex differences, prophylaxis significantly reduced urinary tract infection in boys (P = 0.013), most notably in boys with grade III vesicoureteral reflux (P = 0.042). There were no other differences in outcome based on sex or VUR grade. [28]

Definitions and criteria for diagnosis of initial and recurrent UTI differed between studies and in general were poorly reported. [24] [25] In the systematic review that only looked at children with VUR, the diagnostic definitions/criteria for renal abnormality varied between studies and most of the children had lower grades of VUR; therefore, the review highlighted that care should be taken with extrapolating these results to children with grade V VUR (see Table 1, p 9) and that it is these children who have the highest risk of developing renal scars after pyelonephritis. [25]

The second systematic review noted that, of the five RCTs reporting repeat symptomatic UTI, only one was adequately blinded. Although the result in this study alone was non-significant (14/122 [11%] with prophylaxis *v* 21/121 [17%] with placebo; RR 0.66, 95% CI 0.35 to 1.24), the systematic review concluded that the patient numbers were too small to adequately power this analysis. [25]

The first systematic review found no difference in repeat positive urine culture between antibiotic prophylaxis and placebo/no treatment at 10 weeks to 1 year (4 RCTs, 467 children, 43/270 [16%] with antibiotics *v* 76/197 [39%] with placebo/no treatment, RR 0.31, 95% CI 0.08 to 1.18, P = 0.085; significant heterogeneity, I^2 = 91%, P <0.00001). The heterogeneity was not explained by analysing just the two most recent studies, and the result remained not significant (P = 0.22). [24] The second systematic review also found no difference in repeat positive urine culture at 1 to 3 years with the use of prophylactic antibiotics (6 studies, 636 children, 60/324 [19%] with prophylaxis *v* 73/312 [23%] with no treatment, RR 0.84, 95% CI 0.57 to 1.25, P = 0.40). [25] The first systematic review also queried the appropriateness of this outcome, as few doctors would treat asymptomatic bacteriuria. [24]

Three RCTs in the second systematic review reported results for adherence. [25] One RCT reported 100% adherence, measured by testing the urine sample for the presence of the prophylactic drug in children who developed a febrile UTI. Another RCT found that, while 86% reported compliance according to a visual analogue questionnaire, only 71% of children were adherent when assessed by urine samples. The only placebo-controlled study reporting adherence measured it by weighing the bottles at each clinic visit and direct questioning of the parents. This study reported no difference in the measured non-adherence between groups. [25]

Five studies (4 analysed, 367 children) compared one antibiotic with another, but all compared different combinations or different outcomes and studies were not pooled. Two studies reported microbial resistance, nitrofurantoin having a significantly lower risk of resistance than cotrimoxazole (RR 0.54, 95% CI 0.31 to 0.92). Patients receiving nitrofurantoin were twice as likely to experience side effects (nausea, vomiting, or stomach ache) as patients receiving trimethoprim (RR 2.18, 95% CI 1.39 to 3.41; RD 33%, 95% CI 17 to 50). This suggests that the side effects of nitrofurantoin (NNH = 3, 95% CI 2 to 6) are similar to the prophylactic benefit (NNT = 5, 95% CI 3 to 33) compared with trimethoprim. [24]

We found one RCT, involving 176 children with spina bifida undergoing clean intermittent catheterisation of continuation or discontinuation of low-dose prophylactic antibiotics (previously chosen according to antibiotic resistance patterns; included trimethoprim, nitrofurantoin, cefuroxime, co-trimoxazole, or a combination of antibiotics). [29] Discontinuation led to higher rates of asymptomatic bacteriuria (4.58 per patient-year *v* 3.64 per patient-year; RR 1.25, 95% CI 1.08 to 1.40, P = 0.002) and afebrile UTIs (1.52 per patient-year *v* 1.07 per patient-year; RR 1.44, 95% CI 1.13 to 1.83, P = 0.003), but there was no difference in the number of febrile UTIs (4/88 *v* 2/88, RR 2.0, 95% CI 0.38 to 10.6, P = 0.42).

A systematic review (search date 1990 to 2010) looking at another important subgroup of infants, those with antenatal hydronephrosis, found no RCTs but 21 observational studies (n = 3876). [30] Pooled UTI rates in patients with low-grade hydronephrosis were similar, regardless of continuous antibiotic prophylaxis (CAP) status: 2.2% on prophylaxis versus 2.8% not receiving prophylaxis (P = 0.52). In children with high-grade hydronephrosis, patients receiving CAP had a significantly lower UTI rate versus those not receiving CAP (14.6% *v* 28.9%, P <0.01).

In June 2014, the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial was published. [31] It is not reported in this review, as it was published outside of the search date. However it will be considered for inclusion at the next update.

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Recurrent infection, especially febrile UTI, is thought to be associated with renal parenchymal defects and, therefore, increased risk of future morbidity (e.g., hypertension, chronic renal disease). The low quality of many studies has no doubt contributed to inconsistent findings, but recent larger, high-quality studies appear to show a small reduction in symptomatic UTI and renal parenchymal defects with prophylactic antibiotics. [26] [27] It is unclear whether this applies to all children or whether those with underlying risk factors have most to gain. Although the results from systematic reviews remain unaltered, overall, recent, well-conducted RCTs suggest a limited benefit of prophylaxis: 12 to 13 children need to be treated for 1 year to prevent one symptomatic UTI.

There is no proof that children with VUR benefit significantly from prophylaxis when considering febrile and non-febrile UTIs. There is some evidence of a small reduction in renal scarring: 33 children would need prophylaxis to prevent one extra child developing a new or progressive renal scar over the course of 2 to 3 years. [25] Boys aged under 3 years, particularly those with moderate

(and presumably severe) grades of VUR, may particularly benefit from prophylaxis, but this may reflect the differences in the underlying causes of UTIs. Thus, there remains no convincing evidence to support the routine use of prophylactic antibiotics in children after their first episode of pyelonephritis, or with low to moderate grades of VUR. Prophylaxis to reduce future complications may be warranted in those thought to be at high risk by virtue of a serious presentation, confirmed renal damage, or other factors that predispose to serious recurrences. Nitrofurantoin is less likely to be associated with microbial resistance than co-trimoxazole but is more likely to be associated with adverse effects than trimethoprim. Clinicians may wish to use nitrofurantoin as their first-line prophylactic antibiotic for those children who tolerate it well.

OPTION DIFFERENT DURATIONS OF PROPHYLACTIC ANTIBIOTICS New

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

Benefits: We found no systematic review or RCTs.

Harms: We found no systematic review or RCTs.

Comment: Although we found no systematic reviews or RCTs directly comparing different durations of prophylactic antibiotics, one systematic review [24] reported that a large RCT (576 children; age 0–18 years) showed that 36% of UTIs in the prophylactic antibiotic group and 47% in the placebo group occurred within 3 months of randomisation. [26] A further 19% and 29% (active and placebo arms) occurred at 3 to 6 months. The systematic review inferred that this may suggest an initial course of 3 months' treatment is appropriate, with possible extension to 6 months. [24] However, the actual RCT had duration of treatment of 1 year.

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No study has directly addressed the issue of duration of prophylaxis. The incidence of breakthrough UTIs is greatest soon after commencement of treatment and diminishes over time. A period of 3 to 6 months is, perhaps, an ideal length of time for prophylactic treatment designed to reduce symptomatic UTI. However, prophylaxis is often given to prevent children with VUR suffering complications and, perhaps, resolution or improvement in severity of VUR may be a more suitable determinant of length of treatment in these children, although this has not been adequately considered in any study to date.

GLOSSARY

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.

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.

SUBSTANTIVE CHANGES

Different durations of prophylactic antibiotics New option. Categorised as 'unknown effectiveness'.

Prophylactic antibiotics Two systematic reviews updated. [24] [25] Categorisation changed from 'unlikely to be beneficial' to 'trade-off between benefits and harms'.

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Disclaimer

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

Important outcomes			**Cure of infection, recurrent infection, renal parenchymal defects, adverse effects**						
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of prophylactic antibiotics to prevent recurrent urinary tract infection in children?									
at least 10 RCTs (at least 1069) [24] [25]	Recurrent infection	Prophylactic antibiotics *v* placebo/no treatment	4	0	–1	0	0	Moderate	Consistency point deducted for different results depending on analysis
3 (446) [25]	Renal parenchymal defects	Prophylactic antibiotics *v* placebo/no treatment	4	–1	0	–1	0	Low	Quality point deducted for lack of blinding in two studies; directness point deducted for different durations of antibiotic prophylaxis

Type of evidence: 4 = RCT; 2 = Observational; Consistency: similarity of results across studies. Directness: generalisability of population or outcomes.