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[Intervention Review]

Interventions for primary vesicoureteric reflux

Elisabeth M Hodson[1], Danielle M Wheeler[2], Grahame H Smith[3], Jonathan C Craig[1], Dushyanthi Vimalachandra[4]

[1]Centre for Kidney Research, The Children's Hospital at Westmead, School of Public Health, The University of Sydney, Westmead, Australia. [2]Cochrane Child Health Field, Community Child Health, Sydney Children's Hospital, Randwick, Australia. [3]Department of Urology, The Children's Hospital at Westmead, Westmead, Australia. [4]Kids Health, The Children's Hospital at Westmead, Westmead, Australia

Contact address: Elisabeth M Hodson, Centre for Kidney Research, The Children's Hospital at Westmead, School of Public Health, The University of Sydney, Locked Bag 4001, Westmead, NSW, 2145, Australia. Elisah@chw.edu.au.

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ABSTRACT

Background

Vesicoureteric reflux (VUR) results in urine passing, in a retrograde manner, up the ureter. Urinary tract infections (UTIs) have been considered the main cause of permanent renal parenchymal damage in children with reflux. Management of these children has been directed at preventing infection by antibiotic prophylaxis and/or surgical correction of reflux. Controversy remains as to the optimum strategies.

Objectives

To evaluate the benefits and harms of different treatment options for primary VUR.

Search methods

Randomised controlled trials (RCTs) were identified from the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, reference lists of articles and abstracts from conference proceedings.

Selection criteria

Any treatment of VUR including surgery, antibiotic prophylaxis of any duration, non-invasive techniques and any combination of therapies.

Data collection and analysis

Two authors independently searched the literature, determined study eligibility, assessed quality, extracted and entered data. For dichotomous outcomes, results were expressed as risk ratio (RR) and 95% confidence intervals (CI). Data were pooled using the random effects model.

Main results

Eleven studies (1148 children) were identified. Seven compared correction of VUR (by surgery or endoscope) plus antibiotics for 1-24 months with antibiotics alone, two compared antibiotics with no treatment and two compared different materials for endoscopic correction of VUR. Risk of UTI by 2, 5 and 10 years was not significantly different between surgical and medical groups (2 years RR 1.07, 95% CI 0.32 to 2.09; 5 years RR 0.99, 95% CI 0.79 to 1.26; 10 years RR 1.06, 95% CI 0.78 to 1.44). Combined treatment resulted in a 50% reduction in febrile UTI by 10 years (RR 0.54, 95% CI 0.55 to 0.92) but no concomitant reduction in risk of new or progressive renal damage by 10 years (RR 1.03, 95% CI 0.53 to 2.00). In two small studies no significant differences in risk for UTI (RR 0.75, 95% CI 0.15 to 3.84) or renal damage (RR 1.70, 95% CI 0.36 to 8.07) were found between antibiotic prophylaxis and no treatment.

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Authors' conclusions

It is uncertain whether the treatment of children with VUR confers clinically important benefit. The additional benefit of surgery over antibiotics alone is small at best. Assuming a UTI rate of 20% for children with VUR on antibiotics for five years, nine reimplantations would be required to prevent one febrile UTI, with no reduction in the number of children developing any UTI or renal damage.

PLAIN LANGUAGE SUMMARY

It is unclear whether the identification and treatment of children with vesicoureteric reflux has any clinically important benefit

Vesicoureteric reflux (VUR) is the backflow of urine from the bladder up the ureters to the kidney. People with VUR are thought to be more likely to get urinary tract infections (UTIs) involving the kidney tissue, which may cause permanent kidney damage. Current treatment options include surgery, surgery plus long-term antibiotics, long-term antibiotics alone and endoscopic (injection of a substance around the entry of the ureter into the bladder) correction using different materials. Surgery decreased the number of feverish UTIs, but did not change the number of children developing any UTI or kidney damage. In small studies, antibiotics did not change the number of children developing UTI compared with no treatment. More studies are needed.

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BACKGROUND

Primary vesicoureteric reflux (VUR) is thought to be a maturational abnormality of the vesicoureteric junction, which results in urine passing, in a retrograde manner, up the ureter during voiding. Although the exact prevalence in the general child population is unknown, about a third of children with urinary tract infection (UTI) are consistently found to have VUR (Smellie 1994). UTI occurs in about 5% to 10% of children and about 1% to 3% of children have been reported to suffer from VUR (Hellstrom 1991). VUR is thought to predispose the sufferers to UTIs which involve the kidney substance and, thus, may cause permanent renal injury. Retrospective studies of selected patients with renal scarring report hypertension in about 20% and chronic kidney disease (CKD) in about 10% patients (Martinell 1996; Smellie 1998) though recent data from a prospective cohort study indicate that adverse outcomes of renal damage associated with UTI are considerably lower (Wennerstrom 2000b; Wennerstrom 2000c).

The central management strategy of children with VUR has been the avoidance of UTI-induced damage (Belman 1995). This has been attempted by surgical correction of reflux and long-term antibiotic prophylaxis, either singly or in combination. In addition to the common Politano-Leadbetter and Cohen surgical techniques, new, less invasive techniques which involve endoscopic periureteric injections of polydimethylsiloxane (Macroplastique), dextranomer/hyaluronic acid copolymer (Deflux) or glutaraldehyde cross-linked bovine collagen have been assessed (Capozza 2002; Frankenschmidt 1997; Frey 1997; Oswald 2002).

Although VUR is a common problem in childhood, there is considerable disagreement regarding the best treatment. A review conducted by the Pediatric Vesicoureteral Reflux Guidelines Panel (Elder 1997) resulted in few recommendations for treatment based on scientific evidence of effect, instead relying on "panel opinion" for the majority of decisions. The aims of this study were to evaluate the evidence available for the benefits and harms of the different treatment options currently available: operative, non-operative or no intervention.

OBJECTIVES

To evaluate the evidence for the benefits and harms of the different treatment options for primary VUR.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) which evaluated any treatment in primary VUR.

Types of participants

- Males and females of any age with primary VUR diagnosed by micturating cystourethrogram (MSU) with or without UTI.
- Patients with VUR associated with posterior urethral valves, spina bifida, other urological abnormalities or kidney transplants were excluded.

Types of interventions

Treatments of VUR including surgery (open and endoscopic techniques), antibiotic prophylaxis of any duration, non-invasive techniques such as bladder training and any combination of therapies.

Types of outcome measures

- UTI diagnosed using conventional microbiological criteria, that is > 10^8 colony forming units (cfu)/L on a mid-stream urine sample, or > 10 cfu/L on a sample obtained by catheter or suprapubic bladder tap. Attempts were made to analyse both frequency and duration of infection.
- Renal parenchymal abnormality, controlled for any pre-existing damage and defined as new, progression, resolution, end-stage kidney disease (ESKD), and diagnosed by ultrasound, intravenous pyelography or ^{99m}Tc-DMSA (dimercaptosuccinic acid) scintigraphy.
- Number of previously unaffected subjects who develop hypertension, defined as greater than 140 mm Hg systolic, 90 mm Hg diastolic for adults, above the 95th percentiles for systolic and diastolic blood pressures in children.
- Renal function impairment defined as a corrected glomerular filtration rate (GFR) (measured either directly or calculated from serum creatinine) less than the 95th percentile for age, or a decrease in renal function over the duration of the study.
- Correction of VUR, defined as the number of children and/or ureters without reflux on follow up imaging study.
- Obstruction following correction of VUR, death or serious injury resulting from the anaesthetic, wound infection, fever, adverse effects of medication including urticaria, gastro-intestinal reaction.

Search methods for identification of studies

Initial search

Relevant studies were obtained from the following sources;

- The Cochrane Renal Group Specialised Register (November 2003).
- Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, Issue 4, 2003.
- MEDLINE (1966 to February 2003).
- EMBASE (1988 to February 2003).
- Reference lists of relevant articles, reviews and studies.
- Pharmaceutical industry representatives.
- Known authors in the field.

Search terms for VUR were; (vesico-ureteral reflux.sh) or (vesicoureteral reflux.tw) or (VUR.tw) or (vesico-ureteric reflux.tw) or (vesicoureteric reflux).

There were no language restrictions.

Review update

For this update the Cochrane Renal Group's specialised register (June 2006) and The Cochrane Central Register of Controlled Trials (CENTRAL, in *The Cochrane Library* Issue 2, 2006) was searched. CENTRAL and the Renal Group's specialised register contain the handsearched results of conference proceedings from general and

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speciality meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective (Master List 2007). Please refer to The Cochrane Renal Review Group's Module in *The Cochrane Library* for the complete list of nephrology conference proceedings searched.

Data collection and analysis

Abstracts obtained from the above searches were screened for selection independently by at least two authors (EH, DV, DW). Any disagreements were resolved by discussion with a third author (JC). Where suitability was uncertain or no abstract available, the full article was obtained. In all cases over selection was considered preferable to avoid losing relevant studies and to ensure additional studies could identified from reference lists. Authors were contacted to obtain raw or missing data where necessary.

Data extraction was conducted independently by at least two authors (EH, GS, DV, DW) using a pro forma which recorded methodological quality; randomisation method, allocation concealment, blinding of outcome assessors, intention-to-treat analysis and percentage of subjects lost to follow-up *(*Schulz 1995). Any discrepancies were resolved by discussion with another author (JC). Where the results of a study are published more than once, the results were counted once only in each analysis.

Analysis of the following treatment comparisons was planned:

- antibiotics and placebo;
- antibiotics and surgical or endoscopic correction;
- one antibiotic treatment with another;
- surgical correction and endoscopic correction or one surgical procedure with another surgical procedure;
- surgical or endoscopic correction with no other treatment;
- any combinations of therapy.

For dichotomous outcomes the risk ratio (RR) with 95% confidence interval (CI) were calculated for individual studies and the summary statistics were calculated using a random effects model. The random effects model takes into account between-study variability as well as within-study variability. A fixed effect model was also used to test the robustness of the analysis. Heterogeneity between studies was analysed using Cochran's Q statistic with an α of 0.1 used for statistical significance (Lau 1997) and by I^2 statistic. I^2 is calculated from Cochran Q and describes the percentage of total variation across studies that is due to heterogeneity (Higgins 2003). A value of 0% indicates no observed heterogeneity and larger values indicate increasing heterogeneity.

To determine the effect of study quality, sensitivity analysis had been planned to examine the influence of allocation concealment, blinding and adequacy of follow-up on results.

RESULTS

Description of studies

Full paper assessment originally identified eleven RCTs. The International Reflux Study was reported in two arms, European (IRS EUR 1981-2003) and US (IRS USA 1992), and so has been treated as two separate studies. One study was subsequently excluded because it was not possible to separate the outcomes for randomised patients from those of a non-randomly selected group of children reported in the same publication (Scholtmeijer 1993). Two included studies were identified by review of personal reference lists of the authors and have been published in conference proceedings only (Morris 1991; Reddy 1997). A further search in June 2006 identified one new study (Garin 2006) and two additional reports of the European arm of the International Reflux Study.

Seven studies were identified which compared the effectiveness of long-term antibiotic administration (given for one to five years) with ureteric reimplantation by open surgery (BIRSG 1987; Holland 1982; IRS EUR 1981-2003; IRS USA 1992; Morris 1991; Smellie 2001) or endoscopic subureteric implantation of Dx/HA copolymer (Deflux) (Capozza 2002). In all studies the surgical arm patients received antibiotic prophylaxis for one to 24 months. An eighth study (Reddy 1997) compared no treatment with two antibiotic prophylaxis regimens (daily or intermittent antibiotic administration). Two studies compared different materials for subureteric injection to correct reflux (Frey 1997; Oswald 2002). Garin 2006 compared antibiotic prophylaxis with no specific treatment in children with and without reflux - only the data from children with reflux was included in this review. The 11 studies enrolled 1148 children under the age of 16 years from the USA, Europe and New Zealand. Data for at least one outcome were available from 1059 children. No RCT of any intervention in adults was found. No RCT was identified which compared antibiotics alone with surgery without any period of antibiotic prophylaxis or used other interventions including managements for voiding dysfunction. No RCT comparing an open surgical procedure with endoscopic correction of VUR was identified. A variety of open surgical techniques were used to correct VUR and trimethoprim, trimethoprim/sulphamethoxazole or nitrofurantoin were used for antibiotic chemoprophylaxis. Generally only children with higher (dilating) grades of VUR were included in the studies and outcomes were reported at three months to 10 years post randomisation.

Criteria for UTI (the primary outcome in most studies) were either not given or the microbiological threshold of > 100,000 cfu/mL was used. Symptomatic and asymptomatic UTI were not differentiated except in both arms of the International Reflux Study and Garin 2006, which distinguished between asymptomatic bacteriuria, cystitis or acute pyelonephritis. The latter was a clinical diagnosis and was defined as bacteriuria and fever of at least 38.5°C, loin or back pain, or general fatigue which could not otherwise be explained. Results were expressed as cumulative incidence over one to two years and/or four to five years of follow-up. Data on UTI was available to 10 years in IRS EUR 1981-2003. Four studies (BIRSG 1987; IRS EUR 1981-2003; IRS USA 1992; Smellie 2001) defined renal scarring on intravenous pyelogram as focal thinning of the renal parenchyma overlying a distorted or clubbed calyx. Three studies (IRS EUR 1981-2003; IRS USA 1992; Smellie 2001) also graded scars according to the grading system of Smellie 1975. IRS EUR 1981-2003 and IRS USA 1992 also reported on renal parenchymal thinning, which was defined as thinning of parenchyma by at least -2.5 standard deviation score (SDS) without associated calyceal distortion. Garin 2006 defined acute pyelonephritis as focal or diffuse areas of decreased uptake and renal scarring was defined as decreased uptake with loss of contours of the kidney or cortical thinning with decreased volume on ^{99m}Tc-DMSA scintigraphy. No definition of renal scarring was provided in Capozza 2002 and Holland 1982.

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Risk of bias in included studies

The method of treatment allocation was satisfactory in five studies (Table 1 - *Quality of included tables*). Only two studies reported that assessment of radiological outcomes was determined without knowledge of treatment groups. Intention-to-treat analysis was not performed in four studies; in the remaining studies it was not possible to determine whether the analysis had been done on an intention-to-treat basis. Losses to follow-up were generally low being 0% and 2% at 1 to 2 years and 9% and 42% at 4 to 10 years of follow-up.

Effects of interventions

Reflux correction with surgery plus antibiotics (1-24 months) versus antibiotics alone

We combined the results of studies comparing antibiotic prophylaxis (1 to 5 years) and surgical or endoscopic procedures to correct VUR (with antibiotics for 1 to 24 months) to obtain summary measures of treatment effects. There was no appreciable difference between the summary estimators using random and fixed effects models. The outcomes of UTI and renal parenchymal abnormality did not appear to be heterogeneous (Analysis 1.1, Analysis 1.2), and formal testing for heterogeneity confirmed this. There were insufficient studies to explore potential effect modification using subgroup analysis or meta-regression.

Urinary tract infection

UTI was examined in 7 studies (BIRSG 1987; Capozza 2002; Holland 1982; IRS EUR 1981-2003; IRS USA 1992; Morris 1991; Smellie 2001). The frequency of all forms of recurrent UTI varied between 0% and 42% in the antibiotic-only group and 20% and 22% in surgery plus antibiotic treatment group by 2 years of follow-up. By 2 years, there was no significant reduction in the risk of UTI in the surgery plus antibiotic treatment group compared with the antibiotic-only group (Analysis 1.1.1 (4 studies, 341 patients): RR 1.07, 95% CI 0.55 to 2.09). By 5 years the frequency of all forms of recurrent UTI varied between 29% and 42% in the antibiotic-only group and 25% and 40% in the surgery plus antibiotic treatment group.

Between 0 and 5 years, there was no significant difference in the risk of all UTI between groups (Analysis 1.1.2 (3 studies, 479 children): RR 0.99, 95% CI 0.79 to 1.26). The overall incidence of symptomatic UTI (febrile and non-febrile) was only reported by the European arm and showed no significant difference in risk between groups (IRS EUR 1981-2003). There was no difference in the risk of symptomatic UTI between 0 and 5 years (Analysis 1.1.3 (1 study, 297 children): RR 0.95, 95% CI 0.67 to 1.35), between 5 and 10 years (Analysis 1.1.4 (1 study, 252 children): RR 0.79; 95% CI 0.49 to 1.26) and overall from 0 to 10 years in those children followed for 10 years (Analysis 1.1.5 (1 study, 252 children): RR 1.06; 95% CI 0.78 to 1.44)(IRS EUR 1981-2003). The frequency of febrile UTI was reported only in both arms of the International Reflux Study and was 22% in the antibiotic-only groups and 8% to 10% in the surgery plus antibiotic treatment groups by five years of follow-up. Children in the surgery plus antibiotic treatment group had significantly fewer febrile UTI than the antibiotics alone group between 0 to 5 years (Analysis 1.1.6 (2 studies, 429 children): RR 0.43, 95% CI 0.27 to 0.70) and this persisted between 5 and 10 years (Analysis 1.1.7 (1 study, 252 children): RR 0.34, 95% CI 0.14 to 0.82) so that overall in children followed for 10 years there were significantly fewer febrile UTIs among children undergoing surgery plus antibiotic treatment compared with antibiotics alone (Analysis 1.1.8 (1 study, 252 children): RR 0.54, 95% CI 0.32 to 0.92). The increased risk of febrile infections in the antibiotic-only group was matched by a reduction in risk of afebrile symptomatic infections in the antibiotic-only group compared with the surgical treatment group.

Renal parenchymal abnormality

Renal parenchymal abnormalities were examined in five studies (BIRSG 1987; Holland 1982; IRS EUR 1981-2003; IRS USA 1992; Smellie 2001). The frequency of renal parenchymal abnormality (scars and renal parenchymal thinning) on intravenous pyelogram (IVP) at study entry was 56% to 100% with no difference between medical and surgery plus antibiotic groups. Based on patient data, no significant differences were found for the risks for new renal parenchymal abnormality at 2 years (Analysis 1.2.1 (2 studies, 171 children): RR 1.06, 95% CI 0.33 to 3.42) or 4 to 5 years (Analysis 1.2.2 (4 studies, 572 children): RR 1.09, 95% CI 0.79 to 1.49). Similarly the risks for progression in abnormality (Analysis 1.2.4 (3 studies, 468 children): RR 0.99, 95% CI 0.69 to 1.42) or total new and progressive abnormality (Analysis 1.2.6 (3 studies, 468 children): RR 1.05, 95% CI 0.85 to 1.29) did not differ at 4 to 5 years. Only one small study of 10 patients assessed progression of renal injury at 2 years based on patient data (Analysis 1.2.3, Analysis 1.2.5).

The European and US arms of the International Reflux Study differentiated renal scarring and renal parenchymal thinning on intravenous pyelogram. There were no significant difference in the number of patients with renal scars on IVP at 0 to 5 years (Analysis 1.3.1 (2 studies, 418 children): RR 1.28, 95% CI 0.84 to 1.94), at 5 to 10 years (Analysis 1.3.2 (1 study, 223 children): RR 1.03, 95% CI 0.07 to 16.22) and for 0 to 10 years in children followed for 10 years in the European arm of the International Reflux Study (Analysis 1.3.3 (1 study, 223 children): RR 1.03, 95% CI 0.53 to 2.00)(IRS EUR 1981-2003; IRS USA 1992). In the IRS EUR 1981-2003, renal scarring on IVP was present at entry in 49% of the 306 children originally treated and in 51% of 223 children studied by IVP at 10 years. During the first 5 years of follow-up, 40 children (surgery plus antibiotic group (21), antibiotic group (19)) developed new scars. Of these 28 were among 223 followed radiologically at 10 years. Only two more children, one from each therapy group, developed new scars between 5 and 10 years.

When the data were examined according to the total number of kidneys, there were also no significant differences at 2 years in new (Analysis 1.4.1 (2 studies, 235 children): RR 1.03, 95% CI 0.31 to 3.37), progressive (Analysis 1.4.2 (2 studies, 235 children): RR 1.56, 95% CI 0.24 to 10.08) or total renal parenchymal abnormalities (Analysis 1.4.5 (2 studies, 235 children): RR 1.54, 95% CI 0.24 to 9.95). Similarly the risks for new abnormality (Analysis 1.4.3 (2 studies, 319 children): RR 0.85, 95% CI 0.24 to 3.09), progression in abnormality (Analysis 1.4.4 (2 studies, 319 children): RR 0.84, 95% CI 0.50 to 1.41) or total abnormality (Analysis 1.4.6 (2 studies, 319 children): RR 0.84, 95% CI 0.53 to 1.34) did not differ at 4 to 5 years.

Two studies (Capozza 2002; IRS EUR 1981-2003) ascertained renal parenchymal abnormality using ^{99m}Tc-DMSA scintigraphy. In Capozza 2002, there was no significant difference in the risk of abnormality at one year between medical and surgically treated groups (Analysis 1.5.1 (1 study, 60 children): RR 0.18, 95% CI 0.02 to 1.62) though only four children developed abnormalities. In the IRS EUR 1981-2003 287/297 children had scintigraphy performed

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at 5 years and 216/297 children had scintigraphy performed at 10 years. Parenchymal abnormalities were present in 83% of children at study entry. Relative to the antibiotic-only group, there was no significant increased risk of new or progressive ^{99m}Tc-DMSA scintigraphy abnormalities in the surgery plus antibiotic treatment group (Analysis 1.5.2 (1 study, 287 children): RR 0.97, 95% CI 0.58 to 1.62) or in deterioration in ^{99m}Tc-DMSA appearance between 5-10 years (Analysis 1.5.3 (1 study, 216 children): RR 0.71, 95% CI 0.31 to 1.58).

Renal growth was evaluated in 4 studies (BIRSG 1987; IRS EUR 1981-2003; IRS USA 1992; Smellie 2001) at 2 to 10 years by measurements of changes in renal length SDS (3 studies, 510 children) or renal area (1 study, 82 children) on intravenous pyelogram. No significant differences between groups were found at any time point or in any age group. Combining of data in meta-analysis was not possible because of differences in reporting data.

Other outcomes

Each study reported a number of other outcomes. The two outcomes of greatest clinical importance, ESRD and hypertension, were reported by 3 studies (BIRSG 1987; IRS EUR 1981-2003; Smellie 2001). Six children developed ESRF and 14 developed hypertension during follow-up. There was no significant difference in the risk for ESRD (Analysis 1.6.1 (2 studies, 154 children): RR 1.07, 95% CI 0.23 to 5.04) or hypertension (Analysis 1.6.2 (2 studies, 154 children): RR 0.93, 95% CI 0.25 to 3.42) between treatment groups at 5 years or for hypertension at 10 years (Analysis 1.6.3 (1 study, 252 children): RR 0.15, 95% CI 0.01 to 2.78). Five studies (BIRSG 1987; Capozza 2002; IRS EUR 1981-2003; Morris 1991; Smellie 2001) reported data on GFR but these were unable to be combined because of insufficient reported point estimate and variance data. Individually, no study reported any significant difference between groups. Data from IRS EUR 1981-2003 showed no significant differences in GFR measured by the Schwartz formula at study entry (Analysis 1.7.1), at 5 years (Analysis 1.7.2) and at 10 years (Analysis 1.7.3). Growth was also investigated in IRS EUR 1981-2003. There was no significant difference in height SDS at study entry (Analysis 1.8.1) or at 10 years (Analysis 1.8.2).

Resolution of VUR was an outcome described in five studies but combining of individual study data was not possible because of differences in reporting practices (patients and ureters), not all patients having follow-up MSUs and missing data. In 4 studies (BIRSG 1987; IRS EUR 1981-2003; IRS USA 1992; Smellie 2001) the postoperative resolution rate at 4 to 5 years for ureters was 93% to 99%. Over the same follow-up period between 16% to 49% of patients had spontaneous resolution of VUR (BIRSG 1987; IRS EUR 1981-2003; IRS USA 1992; Smellie 2001). In IRS EUR 1981-2003, 130/155 children in the antibiotic-only group had persisting VUR at 5 years though in 50 other children VUR grade had diminished. Among 102 children undergoing voiding MSUs at 10 years, VUR was still present in 27 children (22 with grade IV and 5 with grade III reflux). The resolution rate of VUR at 12 months for patients after Dx/HA copolymer subureteric implantation was 69% compared with 38% in the antibiotic-only group (Capozza 2002).

Adverse events for either group were generally not well reported. Postoperative obstruction to the urinary tract occurred in 6.6% of children (10/151) in the European arm of the International Reflux Study. The Birmingham Reflux Study stated that no cases of postoperative obstruction were found after 5 years. No other study referred to obstruction. No other adverse outcomes of surgery, including anaesthesia, were reported.

Antibiotic prophylaxis versus surveillance/no treatment

Reddy 1997 randomised children to receive no treatment, daily antibiotic prophylaxis or prophylaxis given on three days each week. Garin 2006 randomised children to receive no treatment or daily antibiotic prophylaxis. There was no significant difference in the risk of UTI between daily antibiotic prophylaxis and no prophylaxis (Analysis 2.1.1 (2 studies, 142 children): RR 0.75, 95% CI 0.15 to 3.84) or between intermittent prophylaxis and no prophylaxis (Analysis 2.1.2 (1 study, 30 children): RR 0.46, 95% CI 0.10 to 2.00). There was no significant difference in the risk of febrile UTI between children on antibiotics or those receiving no treatment (Analysis 2.2.1 (1 study, 113 children): RR 7.38, 95% CI 0.94 to 58.07), though there were few events in either group so confidence intervals were wide. Similarly there was no significant difference in the risk for renal parenchymal injury between daily antibiotic prophylaxis and no prophylaxis (Analysis 2.3.1 (2 studies, 142 children): RR 1.70, 95% CI 0.36 to 8.07) or between intermittent prophylaxis and no prophylaxis (Analysis 2.3.2(1 study, 30 children): RR 0.38, 95% CI 0.02 to 8.59). No data on adverse events were reported.

Different materials for subureteric injection to correct VUR

Oswald 2002 compared endoscopic subureteric injections of polydimethylsiloxane (Macroplastique) with dextranomer/hyaluronic acid copolymer (Deflux). There was no significant difference in the risk for persistent reflux greater than Grade 1 at 3 months (Analysis 3.1.1 (1 study, 114 children): RR 0.48, 95% CI 0.22 to 1.04) and 1 year (Analysis 3.1.2 (1 study, 73 children): RR 0.62, 95% CI 0.28 to 1.40) or in the risk for UTI (Analysis 3.1.4 (1 study, 72 children): RR 1.68, 95% CI 0.52 to 5.44). Temporary pelvicalyceal dilatation was more common following Macroplastique (Analysis 3.1.3 (1 study, 114 children): RR 1.85, 95% CI 1.02 to 3.35). No data on renal parenchymal abnormalities were reported.

Frey 1997 compared endoscopic subureteric injections of different concentrations of cross-linked collagen (GAX 65, GAX 35). Reflux was significantly more likely to persist following GAX 35 than GAX 65 injections (Analysis 3.2.1 (1 study, 28 children): RR 0.21, 95% CI 0.05 to 0.85). Recurrence of reflux was not significantly different between therapies (Analysis 3.2.2 (1 study, 28 children): RR 0.30, 95% CI 0.07 to 1.29). No data on UTIs or renal parenchymal abnormalities were reported.

DISCUSSION

In children with VUR identified following UTI, no significant differences in the risk for UTI or renal parenchymal injury were found in a meta-analysis of seven studies with 847 evaluable patients comparing antibiotic prophylaxis with combined surgery (open or endoscopic) and antibiotics. However the risk for febrile UTI over 10 years was reduced by 50% among surgically treated compared with medically treated children. Two studies involving 142 children found no difference in the risk for UTI or renal parenchymal injury between groups treated with continuous antibiotic prophylaxis compared with no therapy. However, small patient numbers resulted in wide confidence intervals so that differences between groups cannot be excluded. No differences between treatment groups were demonstrated for the end points of

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hypertension and CKD but the studies were not powered to detect these endpoints and follow-up time was too short.

Data from available RCTs of interventions in children with VUR do not provide evidence as to whether the current practice of diagnosing and treating children with VUR confers important health benefits since no adequately powered studies have included a no treatment arm. The diagnosis of VUR is most commonly made after UTI in childhood, when it is widely recommended that children be investigated. With a 5% to 10% cumulative incidence of UTI during childhood, many children will have an MSU performed. This test generally requires urethral catheterisation, which is distressing for the children and their families (Phillips 1998), involves exposure to ionising radiation and may cause UTI. Medical intervention requires the use of long-term antibiotics, which may contribute to the global problem of the development of antibiotic resistant bacteria (Goossens 1998). The diagnosis of VUR may also cause psychological stress to parents and carers of affected children who become concerned and anxious when they are told their children have a "kidney problem" and may be at risk of UTI, renal "scarring", hypertension and CKD. These risks have been regarded as acceptable since the 1960s when the association was made between VUR and renal parenchymal damage. Although there are associations between VUR, UTI and kidney damage, the assumption that VUR is a modifiable risk factor is not based on strong empiric evidence from existing RCTs. In addition, recent data from prospective cohort studies suggest that in approximately 50% children, renal parenchymal abnormalities reflect renal dysplasia associated with dilating VUR rather than damage due to UTI (Wennerstrom 2000a). The belief that children with VUR should be treated with surgery, antibiotics or both developed in the 1960s from animal data which showed that infection in the presence of VUR caused kidney damage. This belief still needs appropriate evaluation with an adequately powered placebo-controlled RCT in children with VUR to determine whether any therapy is effective in preventing significant and progressive renal injury though two small studies have not demonstrated any difference in the risk of symptomatic UTI, febrile UTI or renal parenchymal injury between antibiotic prophylaxis and no therapy.

If VUR were an important modifiable risk factor for the development of UTI and renal parenchymal damage then we would anticipate a significant reduction in these outcomes for the surgery plus antibiotic group relative to the antibiotic-only group. Instead, there was no significant difference in the risk of UTI by 2, 5 or 10 years, and no significant reduction in the risk of new or progressive areas of kidney damage at 5 and 10 years using intravenous pyelography or ^{99}Tc-DMSA scintigraphy. Surgical treatment with variable durations of antibiotic prophylaxis reduced the risk of febrile UTI at 5 and 10 years. Assuming a constant RR, the number of children requiring a reimplantation operation at different baseline risk of recurrent infection can be calculated. If the risk were 20%, about 9 children would need to be treated with reimplantation surgery compared with antibiotics alone to prevent one febrile UTI during the next 5 years. If the risk were 10%, 17 children would need to be treated with surgical therapy to prevent one febrile UTI. These benefits need to be weighed up against the adverse effects of surgery. Of all the outcomes assessed, febrile UTI is the most subjective outcome and is liable to differential misclassification. A randomised comparison between surgical treatment alone and antibiotic treatment has not been performed since in all studies antibiotics were also given for a variable length of time; only studies designed to assess the incremental benefit of surgery over antibiotics alone have been conducted. These show that the incremental benefit of surgery over antibiotics alone is, at best, small and perhaps not worth the potential harms.

Endoscopic subureteric injection of various materials offers an alternative method of correcting VUR assuming that correction is beneficial and is now widely used in North America and Europe since the day stay procedure is associated with less pain and postoperative recovery time compared with open surgery. Two studies included in this review have demonstrated acceptable rates of reflux correction with three different materials. In a systematic review of 63 articles involving 5527 patients, the success rates for correction of VUR grades I and II, III, IV and V were 78.5%, 72%, 63% and 51% after one treatment; second treatments had an overall success rate of 68% (Elder 2006). Therefore rates of correction are lower than those reported with surgical reimplantation techniques particularly for high grade reflux. It remains to be demonstrated whether endoscopic correction of VUR provides a benefit over no treatment particularly in preventing febrile UTIs. This needs to be carefully evaluated in an RCT since the availability of a relatively non-invasive procedure for VUR correction is probably already increasing the number of children, who are undergoing corrective procedures rather than continue antibiotic prophylaxis. If endoscopic correction is demonstrated to be beneficial in preventing febrile UTI, then the benefits of VUR correction in a child with recurrent febrile UTIs could outweigh the risks of the procedure because the procedure is less invasive than open surgical correction.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review of RCTs of interventions for children with VUR has identified a number of important and unanswered questions:

- Most importantly, it is not clear whether any intervention for children with primary VUR does more good than harm.
- Assuming intervention is beneficial, it is not clear whether antibiotics alone or reimplantation surgery alone are most effective in reducing the risk of UTI and renal parenchymal abnormality.
- The studies, which have been undertaken comparing surgery plus antibiotics with antibiotics alone, have not demonstrated any additional benefit of surgery except for a reduction in risk of febrile UTIs.

Paediatricians and general practitioners who care for children need to be aware that existing research data do not provide a firm basis for decision making when they consider how best to investigate children following UTI and treat those with VUR.

Implications for research

Further well designed and adequately powered studies in children with VUR are still required to determine whether any therapy is effective in preventing significant and progressive renal injury:

- The efficacy of antibiotic prophylaxis compared with placebo on febrile and non-febrile UTI and renal parenchymal injury assessed by ^{99m}Tc-DMSA scintigraphy.

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- Correction of ureteric reflux by endoscopic subureteric injection without antibiotic prophylaxis compared with no treatment on the incidence of febrile UTI and renal parenchymal injury assessed by ^{99m}Tc-DMSA scintigraphy.

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REFERENCES

References to studies included in this review

BIRSG 1987 *{published data only}*

Anonymous. A prospective trial of operative versus non-operative treatment of severe vesico-ureteric reflux: 2 years' observation in 96 children. The Birmingham Reflux Study Group. *Contributions to Nephrology* 1984;**39**:169-85. [MEDLINE: 6744870]

Anonymous. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children: five years' observation. Birmingham Reflux Study Group. *British Medical Journal Clinical Research Ed* 1987;**295**(6592):237-41. [MEDLINE: 2888509]

Anonymous. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux: two years observation in 96 children. *British Medical Journal Clinical Research Ed* 1983;**287**(6386):171-4. [MEDLINE: 6409239]

Capozza 2002 *{published data only}*

Capozza N, Caione P. Dextranomer/hyaluronic acid copolymer implantation for vesico-ureteral reflux: a randomized comparison with antibiotic prophylaxis. *Journal of Pediatrics* 2002;**140**(2):230-4. [MEDLINE: 11865276]

Frey 1997 *{published data only}*

Frey P, Gudinchet F, Jenny P. GAX 65: new injectable cross-linked collagen for the endoscopic treatment of vesicoureteral reflux--a double-blind study evaluating its efficiency in children. *Journal of Urology* 1997;**158**(3 Pt 2):1210-2. [MEDLINE: 9258175]

Garin 2006 *{published data only}*

* Garin EH, Olavarra F, Garicia Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. *Pediatrics* 2006;**117**(3):626-32. [MEDLINE: 16510640]

Holland 1982 *{published data only}*

Holland NH, Kazee M, Duff D, McRoberts JW. Antimicrobial prophylaxis in children with urinary tract infection and vesicoureteral reflux. *Reviews of Infectious Diseases* 1982;**4**(2):467-74. [MEDLINE: 6981165]

IRS EUR 1981-2003 *{published data only}*

Hjalmas K, Lohr G, Tamminen-Mobius T, Seppanen J, Olbing H, Wikstrom S. Surgical results in the International Reflux Study in Children (Europe). *Journal of Urology* 1992;**148**(5 Pt 2):1657-61. [MEDLINE: 1433583]

International Reflux Study. Comparison of conservative and surgical treatment of the vesico-uretero-renal reflux. International prospective reflux study in children [Vergleich von medikamentoser und chirurgischer Behandlung beim primaren vesiko-uretero-renalen reflux]. *Urologe (Ausg. A)* 1981;**20**(2):107-15. [MEDLINE: 7025416]

Jodal U, Koskimies O, Hanson E, Lohr G, Olbing H, Smellie J, et al. Infection pattern in children with vesicoureteral reflux randomly allocated to operation or long-term antibacterial prophylaxis. The International Reflux Study in Children. *Journal of Urology* 1992;**148**(5 Pt 2):1650-2. [MEDLINE: 1433581]

Jodal U, Smellie JM, Lax H, Hoyer PF. Ten-year results of randomized treatment of children with severe vesicoureteral reflux. Final report of the International Reflux Study in Children. *Pediatric Nephrology* 2006;**21**(6):785-92. [MEDLINE: 16565873]

Olbing H. Comparison of the surgical and nonsurgical treatment of primary vesico-ureteral-renal reflux--an international reflux study. *Kinderarztliche Praxis* 1986;**54**(9):493-9. [MEDLINE: 3540424]

Olbing H, Claesson I, Ebel KD, Seppanen U, Smellie JM, Tamminen-Mobius T, et al. Renal scars and parenchymal thinning in children with vesicoureteral reflux: a 5-year report of the International Reflux Study in Children (European branch). *Journal of Urology* 1992;**148**(5 Pt 2):1653-6. [MEDLINE: 1433582]

Olbing H, Hirche H, Koskimies O, Lax H, Seppanen U, Smellie JM, et al. Renal growth in children with severe vesicoureteral reflux: 10-year prospective study of medical and surgical treatment: the International Reflux Study in Children (European branch). *Radiology* 2000;**216**(3):731-7. [MEDLINE: 10966703]

Olbing H, Smellie JM, Jodal U, Lax H. New renal scars in children with severe VUR: a 10-year study of randomized treatment. *Pediatric Nephrology* 2003;**18**(11):1128-31. [MEDLINE: 14523634]

Piepsz A, Tamminen-Mobius T, Reiners C, Heikkila J, Kivisaari A, Nilsson NJ, et al. Five-year study of medical or surgical treatment in children with severe vesico-ureteral reflux dimercaptosuccinic acid findings. International Reflux Study Group in Europe. *European Journal of Pediatrics* 1998;**157**(9):753-8. [MEDLINE: 9776536]

Smellie JM, Tamminen-Mobius T, Olbing H, Claesson I, Wikstad I, Jodal U, et al. Radiologic findings in the kidney of children with severe reflux. Five-year comparative study of conservative and surgical treatment. *Urologe (Ausg. A)* 1993;**32**(1):22-9. [MEDLINE: 8447041]

Smellie JM, Tamminen-Möbius T, Olbing H, Claësson I, Wikstad I, Jodal U, et al. Five-year study of medical or surgical treatment in children with severe reflux: radiological renal findings. The International Reflux Study in Children. *Pediatric Nephrology* 1992;**6**(3):223-30. [MEDLINE: 1616829]

Tamminen-Mobius T, Brunier E, Ebel KD, Lebowitz R, Olbing H, Seppanen U, et al. Cessation of vesicoureteral reflux for 5 years in infants and children allocated to medical treatment. The International Reflux Study in Children. *Journal of Urology* 1992;**148**(5 Pt 2):1662-6. [MEDLINE: 1433584]

Wingen AM, Koskimies O, Olbing H, Seppanen J, Tamminen-Mobius T. Growth and weight gain in children with vesicoureteral reflux receiving medical versus surgical treatment: 10-year results of a prospective, randomized study. International Reflux Study in Children (European Branch). *Acta Paediatrica* 1999;**88**(1):56-61. [MEDLINE: 10090549]

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

IRS USA 1992 *{published data only}*

Duckett JW, Walker RD, Weiss R. Surgical results: International Reflux Study in Children--United States branch. *Journal of Urology* 1992;**148**(5 Pt 2):1674-5. [MEDLINE: 1433586]

Weiss R, Duckett J, Spitzer A. Results of a randomized clinical trial of medical versus surgical management of infants and children with grades III and IV primary vesicoureteral reflux (United States). The International Reflux Study in Children. *Journal of Urology* 1992;**148**(5 Pt 2):1667-73. [MEDLINE: 1433585]

Weiss R, Tamminen-Mobius T, Koskimies O, Olbing H, Smellie JM, Hirche H, et al. Characteristics at entry of children with severe primary vesicoureteral reflux recruited for a multicenter, international therapeutic trial comparing medical and surgical management. The International Reflux Study in Children. *Journal of Urology* 1992;**148**(5 Pt 2):1644-9. [MEDLINE: 1433580]

Morris 1991 *{published data only}*

Morris MC, Rothwell DL, Paykel AD. A prospective study of vesico-ureteric reflux and renal function in children [abstract]. Second CJ Hodson Symposium on Reflux Nephrolopathy; 1991; Christchurch (New Zealand). 1991.

Oswald 2002 *{published data only}*

Oswald J, Riccabona M, Lusuardi L, Bartsch G, Radmayr C. Prospective comparison and 1-year follow-up of a single endoscopic subureteral polydimethylsiloxane versus dextranomer/hyaluronic acid copolymer injection for treatment of vesicoureteral reflux in children. *Urology* 2002;**60**(5):894-7. [MEDLINE: 12429323]

Reddy 1997 *{published data only}*

Reddy PP, Evans MT, Hughes PA, Dangman B, Cooper J, Lepow ML, et al. Antimicrobial prophylaxis in children with vesico-ureteral reflux: a randomized prospective study of continuous therapy vs intermittent therapy vs surveillance [abstract]. *Pediatrics* 1997;**100**(3S):555-6. [CENTRAL: CN-00427967]

Smellie 2001 *{published data only}*

* Smellie JM, Barratt TM, Chantler C, Gordon I, Prescod NP, Ransley PG, et al. Medical versus surgical treatment in children with severe bilateral vesicoureteric reflux and bilateral nephropathy: a randomised trial. *Lancet* 2001;**357**(9265):1329-33. [MEDLINE: 11343739]

References to studies excluded from this review

Becker 2004 *{published data only}*

Becker T, Steffens J, Heidenreich A. Pro and contra -- vesicoureteral reflux in childhood -- endoscopic administration vs. open reconstruction. *Aktuelle Urologie* 2004;**35**(4):275-8. [MEDLINE: 15459862]

Osman 2004 *{published data only}*

Osman Y, Abol-Enein H, Nabeeh A, Gaballah M, Bazeed M. Long-term results of a prospective randomized study comparing two different antireflux techniques in orthotopic bladder substitution. *European Urology* 2004;**45**(1):82-6. [MEDLINE: 14667521]

Roseau 2001 *{published data only}*

Roseau E. Vesico-ureteral reflux and nephropathy in the child: medical or surgical treatment?. *Presse Medicale* 2001;**30**(23):1157-8. [MEDLINE: 11505836]

Scholtmeijer 1993 *{published data only}*

* Scholtmeijer RJ. Treatment of vesicoureteric reflux. Results of a prospective study. *British Journal of Urology* 1993;**71**(3):346-9. [MEDLINE: 8477320]

References to ongoing studies

Ransley 2004 *{published data only}*

Ransley PG. Clinical trial of deflux for endoscopic correction of severe vesicoureteric reflux and the effects on improving bladder function outcome. National Research Register UK (www.nrr.nhs.uk/) 2004. [NRR: N0012116994]

Additional references

Belman 1995

Belman AB. A perspective on vesicoureteral reflux. *Urologic Clinics of North America* 1995;**22**(1):139-50. [MEDLINE: 7855950]

Elder 1997

Elder JS, Peters CA, Arant BS Jr, Ewalt DH, Hawtrey CE, Hurwitz RS, et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. *Journal of Urology* 1997;**157**(5):1846-51. [MEDLINE: 9112544]

Elder 2006

Elder JS, Diaz M, Caldamone A, Cendron M, Greenfield S, Hurwitz R, et al. Endoscopic therapy for vesicoureteral reflux: a meta-analysis. I. Reflux resolution and urinary tract infection. *Journal of Urology* 2006;**175**(2):716-22. [MEDLINE: 16407037]

Frankenschmidt 1997

Frankenschmidt A, Katzenwadel A, Zimmerhackl LB, Sommerkamp H. Endoscopic treatment of reflux by subureteric collagen injection: critical review of 5 years' experience. *Journal of Endourology* 1997;**11**(5):343-8. [MEDLINE: 9355951]

Goossens 1998

Goossens H, Sprenger MJ. Community acquired infections and bacterial resistance. *BMJ* 1998;**317**(7159):654-7. [MEDLINE: 9727998]

Hellstrom 1991

Hellstrom A, Hanson E, Hansonn S, Hjalmas K, Jodal U. Association between urinary symptoms at 7 years old and previous urinary tract infection. *Archives of Disease in Childhood* 1991;**66**(2):232-4. [MEDLINE: 2001110]

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Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Lau 1997

Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Annals of Internal Medicine* 1997;**127**(9):820-6. [MEDLINE: 9382404]

Martinell 1996

Martinell J, Lidin-Janson G, Jagenburg R, Sivertsson R, Claesson I, Jodal U. Girls prone to urinary infections followed into adulthood. Indices of renal disease. *Pediatric Nephrology* 1996;**10**(2):139-42. [MEDLINE: 8703696]

Master List 2007

United States Cochrane Center. Master list of journals being searched. http://apps1.jhsph.edu/cochrane/masterlist.asp (accessed May 2007).

Phillips 1998

Phillips DA, Watson AR, MacKinlay D. Distress and the micturating cystourethrogram: does preparation help?. *Acta Paediatrica* 1998;**87**(2):175-9. [MEDLINE: 9512204]

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408-12. [MEDLINE: 7823387]

Smellie 1975

Smellie J, Edwards D, Hunter N, Normand IC, Prescod N. Vesico-ureteric reflux and renal scarring. *Kidney International - Supplement* 1975;**4**:S65-72. [MEDLINE: 1104981]

Smellie 1994

Smellie JM, Poulton A, Prescod NP. Retrospective study of children with renal scarring associated with reflux and urinary infection. *BMJ* 1994;**308**(6938):1193-6. [MEDLINE: 8180534]

Smellie 1998

Smellie JM, Prescod NP, Shaw PJ, Risdon RA, Bryant TN. Childhood reflux and urinary infection: a follow-up of 10-41 years in 226 adults. *Pediatric Nephrology* 1998;**12**(9):727-36. [MEDLINE: 9874316]

Wennerstrom 2000a

Wennerstrom M, Hansson S, Jodal U, Stokland E. Primary and acquired renal scarring in boys and girls with urinary tract infection. *Journal of Pediatrics* 2000;**136**(1):30-4. [MEDLINE: 10636970]

Wennerstrom 2000b

Wennerstrom M, Hansson S, Jodal U, Sixt R, Stokland E. Renal function 16 to 26 years after the first urinary tract infection in childhood. *Archives of Pediatrics & Adolescent Medicine* 2000;**154**(4):339-45. [MEDLINE: 10768669]

Wennerstrom 2000c

Wennerstrom M, Hansson S, Hedner T, Himmelmann A, Jodal U. Ambulatory blood pressure 16-26 years after the first urinary tract infection in childhood. *Journal of Hypertension* 2000;**18**(4):485-91. [MEDLINE: 10779101]

References to other published versions of this review

Wheeler 1999

Wheeler D, Vimalachandra D, Roy P, Smith G, Craig JC. Interventions for primary vesicoureteric reflux. *Cochrane Database of Systematic Reviews* 1999, Issue 2. [DOI: 10.1002/14651858.CD001532]

Wheeler 2003

Wheeler D, Vimalachandra D, Hodson EM, Roy LP, Smith G, Craig JC. Antibiotics and surgery for vesicoureteric reflux: a meta-analysis of randomised controlled trials. *Archives of Disease in Childhood* 2003;**88**(8):688-94. [MEDLINE: 12876164]

Wheeler 2004

Wheeler DM, Vimalachandra D, Hodson EM, Smith GH, Craig JC. Interventions for primary vesicoureteric reflux. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD001532.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

BIRSG 1987

Methods	Country: UK Setting: GP, paediatrician referrals, hospital casualty
Participants	Number: 179 children enrolled, 161 evaluated Age: < 15 years INCLUSION CRITERIA Primary reflux grade II with scarring or grade III, IV, V in absence of UTI within last 12 months

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BIRSG 1987 *(Continued)*

	EXCLUSION CRITERIA Reflux secondary to obstruction or neurogenic bladder
Interventions	ANTIBIOTIC GROUP Trimethoprim or nitrofurantoin 1-2 mg/kg Antibiotics given for 2 year if resolution of reflux or 5 years COMBINED GROUP Surgical reimplantation and antibiotics Antibiotics given for 2 years
Outcomes	1. UTI - culture positive 2. Renal damage on IVP and DMSA scan 3. GFR 4. Resolution of reflux 5. Renal length on IVP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Capozza 2002

Methods	Country: Italy Source: University teaching hospital
Participants	Number: 61 children enrolled, 60 evaluated Age: > 1 year INCLUSION CRITERIA Primary reflux grade II-IV for at least 6 months EXCLUSION CRITERIA Recurrent UTI, duplex systems, neurogenic bladder
Interventions	ANTIBIOTIC GROUP Not specified Antibiotics given for 1 year COMBINED GROUP Subureteric implantation of Dx/HA copolymer (Deflux) and antibiotics Antibiotics given for 1 month
Outcomes	1. UTI 2. Renal damage on ultrasound and DMSA scintigraphy 3. GFR (change) 4. Resolution of reflux
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

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Capozza 2002 *(Continued)*

Allocation concealment?	Low risk	A - Adequate

Frey 1997

Methods	Country: Switzerland Source: University hospital
Participants	Number: 18 children Age: 1.1-10.7 years (average 4.6 years) INCLUSION CRITERIA Primary ureteric reflux; grades I-III EXCLUSION CRITERIA: NS
Interventions	GROUP 1 Subureteric implantation of GAX 65 GROUP 2 Subureteric implantation of GAX 35
Outcomes	1. Correction of reflux 2. Recurrence of reflux
Notes	Data on ureters not patients presented

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Garin 2006

Methods	Country: USA, Chile, Spain Setting/Design: Multicentre study/parallel groups Time frame: December 1998 to December 2003 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 1 year Loss to follow-up: 9% of 236 children with or without VUR did not complete follow-up & were excluded from analysis
Participants	INCLUSION CRITERIA Acute pyelonephritis (fever 38.5C, pyuria, > 100,000 colonies/mL) defined as focal/diffuse areas of decreased uptake on DMSA scan performed 2-7 days after UTI diagnosis 113 analysed children had VUR; 105 analysed children had no VUR TREATMENT GROUP Number: 55 with VUR

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Garin 2006 *(Continued)*

	Age: Median 3 years (range 3 months to 12 years) Sex (M/F): 9/46 CONTROL GROUP Number: 58 with VUR Age: Median 2 years (range 3 months to 9 years) Sex (M/F): 13/45 EXCLUSIONS VUR grade IV or V, neurogenic bladder, posterior urethral valves, urinary diversion, bladder diverticulum, ureterocoele, renal failure, pregnancy
Interventions	TREATMENT GROUP Sulfamethoxazole/trimethoprim (1-2 mg/kg/d trimethoprim) or nitrofurantoin (1.5 mg/kg/d) for 12 months CONTROL GROUP No specific therapy CO-INTERVENTIONS: NS
Outcomes	1. Recurrence of UTI 2. Type of recurrence: cystitis (definition not provided) or pyelonephritis 3. Development of renal scars on DMSA scintigraphy
Notes	Study included children with or without VUR. Stratified before randomisation. Only patients with VUR included Urine screened 3 monthly EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: NS STOP OR END POINT/S: NS ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Holland 1982

Methods	Country: USA Source: NS
Participants	Number: 10 children; all evaluated Age: mean 4.75 years (range 2 months to 10 years) INCLUSION CRITERIA Primary reflux grades II-IV EXCLUSION CRITERIA Secondary reflux, hypertension, renal dysfunction
Interventions	ANTIBIOTIC GROUP Trimethoprim-sulfamethoxazole or nitrofurantoin 1 mg/kg COMBINED GROUP Surgical reimplantation (technique - NS) and antibiotics

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Holland 1982 *(Continued)*

Outcomes	1. UTI - culture positive 2. Renal damage on IVP 3. Adverse effects of antibiotics
Notes	Duration of antibiotics in both groups: mean 17 months (range 5-36 months)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

IRS EUR 1981-2003

Methods	Country: Europe Source: University teaching hospitals
Participants	Number: 321 children; 302 evaluated Age: 6 days to 11 years INCLUSION CRITERIA Primary reflux grade III-IV EXCLUSION CRITERIA Primary reflux grades I-II, major urinary tract abnormality, previous urinary tract surgery, renal dysfunction
Interventions	ANTIBIOTIC GROUP Nitrofurantoin or trimethoprim 1-2 mg/kg continued till resolution of reflux or 5 years COMBINED GROUP PL, Cohen, LG and antibiotics continued for 6 months
Outcomes	1. UTI - culture positive 2. Renal damage on IVP and DMSA scan 3. Obstruction post-op 4. Resolution of reflux 5. Renal length on IVP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

IRS USA 1992

Methods	Country: USA Source: University teaching hospitals
Participants	Number: 142 children; 132 evaluated Age: < 10 years

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IRS USA 1992 *(Continued)*

	INCLUSION CRITERIA Primary reflux grade III-IV EXCLUSION CRITERIA Major urinary tract abnormality, previous urinary tract surgery, renal dysfunction
Interventions	ANTIBIOTICS GROUP Nitrofurantoin or trimethoprim 1-2 mg/kg Antibiotics given till resolution of reflux or 5 years COMBINED GROUP PL, Cohen, or other reimplantation and antibiotics Antibiotics given for 6 months
Outcomes	1. UTI - culture positive 2. Renal damage on IVP 3. Resolution of reflux 4. Renal area on IVP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Morris 1991

Methods	Country: New Zealand Source: NS
Participants	Number: 138 children; 118 evaluated Age: 6 months to 10 years INCLUSION CRITERIA Primary reflux grade III - IV EXCLUSION CRITERIA Major urological abnormality
Interventions	ANTIBIOTIC GROUP Type and dose: NS Antibiotics for 2 years COMBINED GROUP Cohen reimplantation and antibiotics Antibiotics for 3 months
Outcomes	1. UTI - culture positive 2. GFR 3. Resolution of reflux
Notes	

Risk of bias

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Morris 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Oswald 2002

Methods	Country: Austria Source: University urological department
Participants	GROUP 1 Number: 34 children Sex: 10 boys Age: mean 33 months GROUP 2 Number: 36 children Sex: 6 boys Age: mean 36 months INCLUSION CRITERIA Primary reflux grades II-IV EXCLUSION CRITERIA Duplex systems, failed surgical reimplantation, neurogenic bladder, voiding dysfunction
Interventions	GROUP 1 Subureteric injection of polydimethylsiloxane (Macroplastique) GROUP 2 Subureteric injection of Dx/HA copolymer (Deflux)
Outcomes	1. Correction of reflux 2. UTI 3. Adverse effects
Notes	All evaluated Data provided according to ureters for reflux correction

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Reddy 1997

Methods	Country: USA Source: University teaching hospital
Participants	Number: 43 children; all evaluated Age: NS INCLUSION CRITERIA Primary reflux grade not stated, newly diagnosed

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Reddy 1997 *(Continued)*

	EXCLUSION CRITERIA: NS
Interventions	GROUP 1 Antibiotic prophylaxis Antibiotic: NS Antibiotic treatment given for 1 year GROUP 2 Intermittent antibiotics - given on Mondays, Wednesdays and Fridays Daily urine nitrate testing Antibiotic treatment given for 1 year GROUP 3 No antibiotics Surveillance with daily urine nitrate
Outcomes	1. UTI 2. Renal damage on DMSA 3. Resolution of reflux
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Smellie 2001

Methods	Country: UK Source: University teaching hospitals
Participants	Number: 53 children; 50 evaluated Age: 1-12 years INCLUSION CRITERIA Primary reflux grade III-V, renal scarring on IVP EXCLUSION CRITERIA Major urological abnormality
Interventions	ANTIBIOTIC GROUP Nitrofurantoin or trimethoprim or trimethoprim-sulfamethoxazole 1-2 mg/kg Variable duration of antibiotics COMBINED GROUP Cohen procedure and antibiotics 6 months of antibiotics
Outcomes	1. UTI - culture positive 2. Renal damage on IVP 3. GFR (change) 4. Renal length (change)
Notes	

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Smellie 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Reimplantation: PL = Politano-Leadbetter procedure, Cohen = Cohen procedures, LG = Lich-Gregoir procedure
IVP: Intravenous pyelogram
DMSA scan: 99m-techetium dimercaptosuccinic acid scan
Dx/HA copolymer: Dextranomer/hyaluronic acid copolymer
GAX 65 and 35: Cross-linked collagen with 65mg/ml and 35mg/ml of collagen
GFR: glomerular filtration rate
NS: not stated
UTI: urinary tract infection

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

Study	Reason for exclusion
Becker 2004	Review article of the pros and cons of VUR treatment
Osman 2004	RCTs comparing antireflux procedures in ileal bladders
Roseau 2001	French summary of Smellie 2001
Scholtmeijer 1993	Unable to differentiate randomised from non-randomised patients

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

Ransley 2004

Trial name or title	Clinical trial of deflux for endoscopic correction of severe vesicoureteric reflux and the effects on improving bladder function outcome
Methods	
Participants	Children
Interventions	Endoscopic injection of deflux
Outcomes	Cure or downgrading of VUR, improve early outcome of bladder infection
Starting date	May 2001
Contact information	
Notes	Closed April 2006

DATA AND ANALYSES

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Comparison 1. Reflux correction with surgery plus antibiotics (1-24 months) versus antibiotics alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Urinary tract infection	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 All UTI by 1-2 years	4	341	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.55, 2.09]
1.2 All UTI by 4-5 years	3	479	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.79, 1.26]
1.3 All symptomatic UTI by 4-5 years	1	297	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.67, 1.35]
1.4 All symptomatic UTI between 5-10 years	1	252	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.49, 1.26]
1.5 All symptomatic UTI in children followed for 10 years	1	252	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.78, 1.44]
1.6 Febrile UTI by 5 years	2	429	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.27, 0.70]
1.7 Febrile UTI between 5-10 years	1	252	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.14, 0.82]
1.8 Febrile UTI in children followed for 10 years	1	252	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.32, 0.92]
2 Patient data: Renal parenchymal defects (scars & thinning) on IVP	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 New defects at 2 years	2	171	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.33, 3.42]
2.2 New defects (scars and thinning of parenchyma) at 4-5 years	4	572	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.79, 1.49]
2.3 Progression of existing defects at 2 years	1	10	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.45, 108.26]
2.4 Progression of existing defects (scars and parenchymal thinning) at 4-5 years	3	468	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.69, 1.42]
2.5 Total new and progressive renal parenchymal defects at 2 years	1	10	Risk Ratio (M-H, Random, 95% CI)	9.00 [0.61, 133.08]
2.6 Total new and progressive renal parenchymal defects at 4-5 years	3	468	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.85, 1.29]
3 Patient data: Renal scars on IVP	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 New scars at 4-5 years	2	418	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.84, 1.94]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 New scars developing by 5-10 years in children followed for 10 years	1	223	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.07, 16.22]
3.3 New scars at 10 years in children followed for 10 years	1	223	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.53, 2.00]
4 Individual kidney data: Renal parenchymal defects on IVP	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 New defects at 2 years	2	235	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.31, 3.37]
4.2 Progression of existing defects at 2 years	2	235	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.24, 10.08]
4.3 New defects at 4-5 years	2	319	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.24, 3.09]
4.4 Progression of existing defects at 4-5 years	2	319	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.50, 1.41]
4.5 Total new and progressive defects at 2 years	2	235	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.24, 9.95]
4.6 Total new and progressive defects at 4-5 years	2	319	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.53, 1.34]
5 Renal parenchymal defects on DMSA scintigraphy	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Patient data at 1 year	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Patient data at 5 years	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Deterioration in DMSA between 5-10 years	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Outcomes of hypertension and kidney failure	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 End-stage kidney failure	2	154	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.23, 5.04]
6.2 Hypertension	2	154	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.25, 3.42]
6.3 Hypertension at 10 years	1	252	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.78]
7 GFR measured by Schwartz formula	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 GFR at entry	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 GFR at 5 years	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 GFR at 10 years	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

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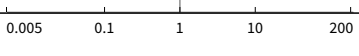
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Height SDS	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8.1 Height Standard Deviation Score at entry	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Height Standard Deviation Score at 10 year follow-up	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Reflux correction with surgery plus antibiotics (1-24 months) versus antibiotics alone, Outcome 1 Urinary tract infection.

Study or subgroup	Surgery + antibiotic n/N	Antibiotics alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 All UTI by 1-2 years					
BIRSG 1987	16/73	23/80		54.9%	0.76[0.44,1.33]
Capozza 2002	6/39	0/21		3.77%	7.15[0.42,121.04]
Holland 1982	1/5	2/5		6.95%	0.5[0.06,3.91]
Morris 1991	13/60	8/58		34.38%	1.57[0.7,3.51]
Subtotal (95% CI)	**177**	**164**		**100%**	**1.07[0.55,2.09]**
Total events: 36 (Surgery + antibiotic), 33 (Antibiotics alone)					
Heterogeneity: Tau^2=0.16; Chi^2=4.59, df=3(P=0.2); I^2=34.59%					
Test for overall effect: Z=0.19(P=0.85)					
1.1.2 All UTI by 4-5 years					
IRS EUR 1981-2003	59/147	59/150		49.65%	1.02[0.77,1.35]
IRS USA 1992	21/64	20/68		32.46%	1.12[0.67,1.85]
Smellie 2001	6/24	11/26		17.89%	0.59[0.26,1.35]
Subtotal (95% CI)	**235**	**244**		**100%**	**0.99[0.79,1.26]**
Total events: 86 (Surgery + antibiotic), 90 (Antibiotics alone)					
Heterogeneity: Tau^2=0; Chi^2=1.76, df=2(P=0.42); I^2=0%					
Test for overall effect: Z=0.04(P=0.97)					
1.1.3 All symptomatic UTI by 4-5 years					
IRS EUR 1981-2003	43/147	46/150		100%	0.95[0.67,1.35]
Subtotal (95% CI)	**147**	**150**		**100%**	**0.95[0.67,1.35]**
Total events: 43 (Surgery + antibiotic), 46 (Antibiotics alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.27(P=0.79)					
1.1.4 All symptomatic UTI between 5-10 years					
IRS EUR 1981-2003	24/125	31/127		100%	0.79[0.49,1.26]
Subtotal (95% CI)	**125**	**127**		**100%**	**0.79[0.49,1.26]**
Total events: 24 (Surgery + antibiotic), 31 (Antibiotics alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1(P=0.32)					
1.1.5 All symptomatic UTI in children followed for 10 years					



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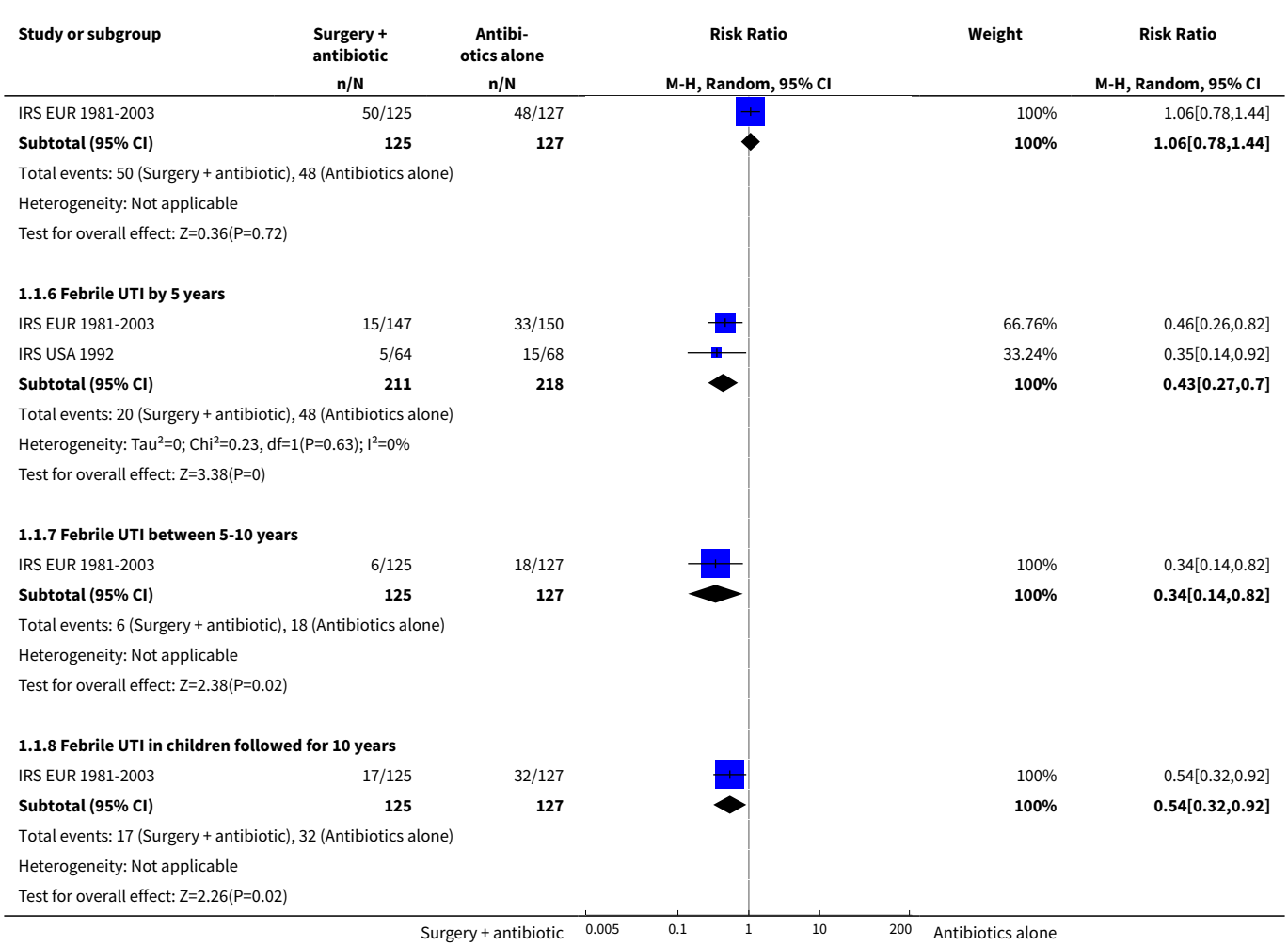
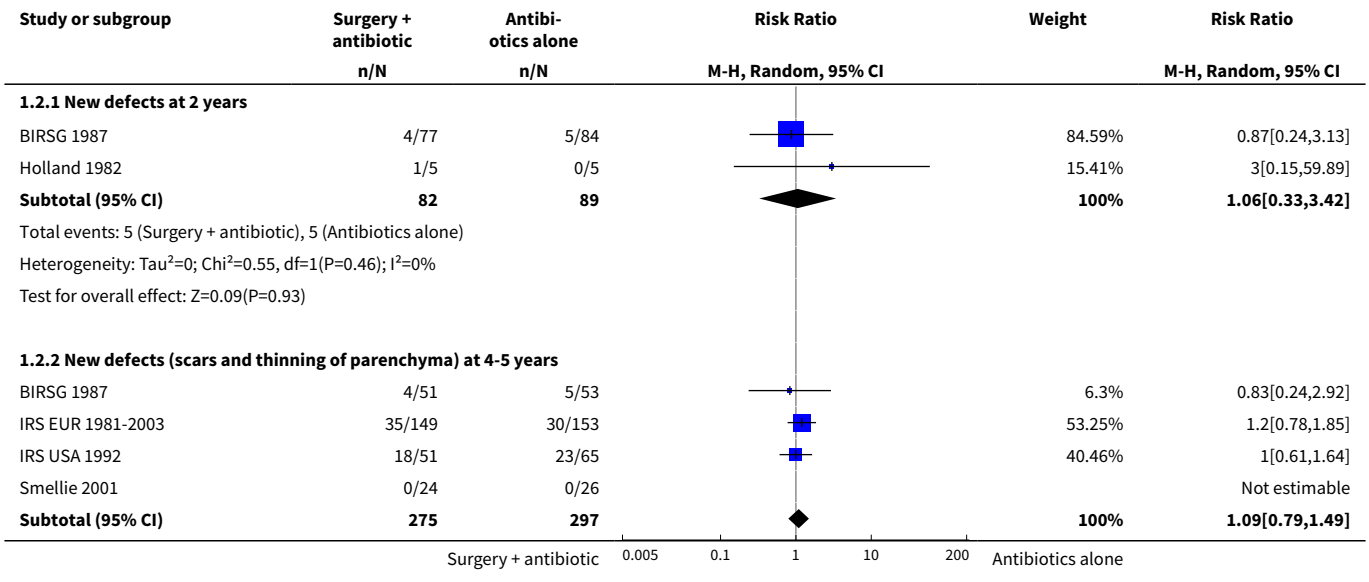


Analysis 1.2. Comparison 1 Reflux correction with surgery plus antibiotics (1-24 months) versus antibiotics alone, Outcome 2 Patient data: Renal parenchymal defects (scars & thinning) on IVP.



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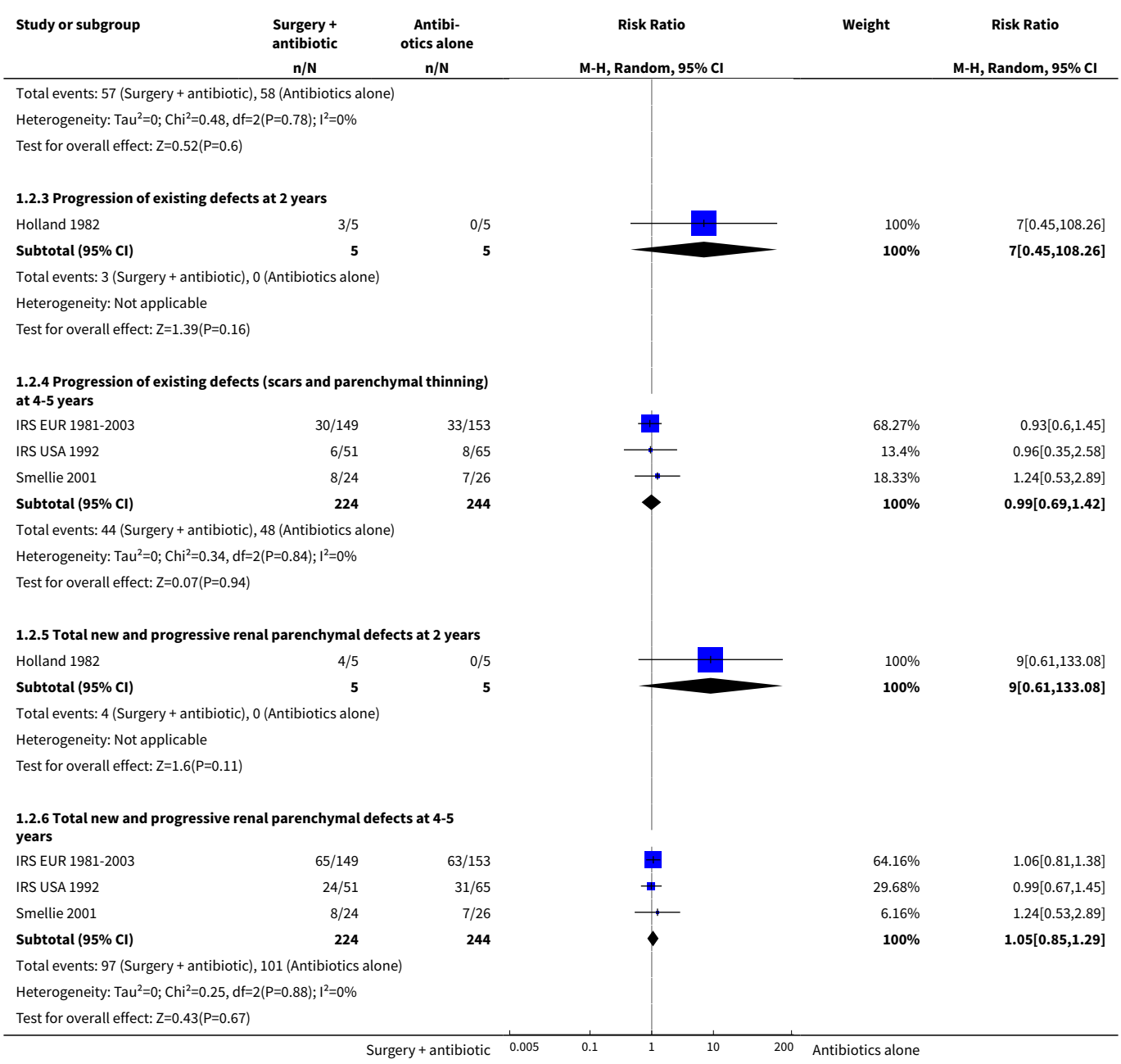
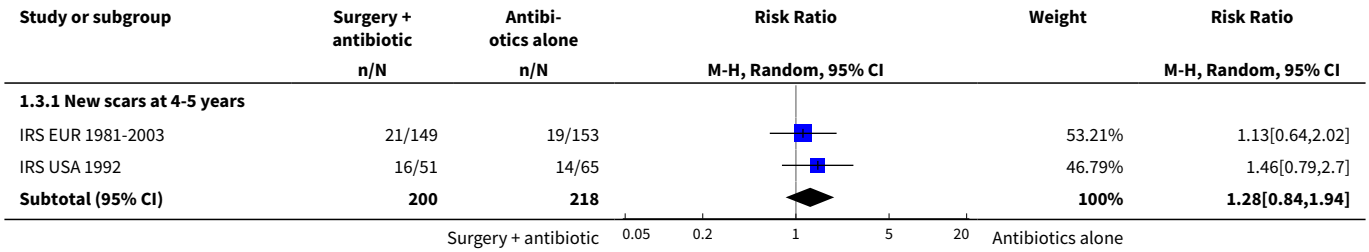


Analysis 1.3. Comparison 1 Reflux correction with surgery plus antibiotics (1-24 months) versus antibiotics alone, Outcome 3 Patient data: Renal scars on IVP.



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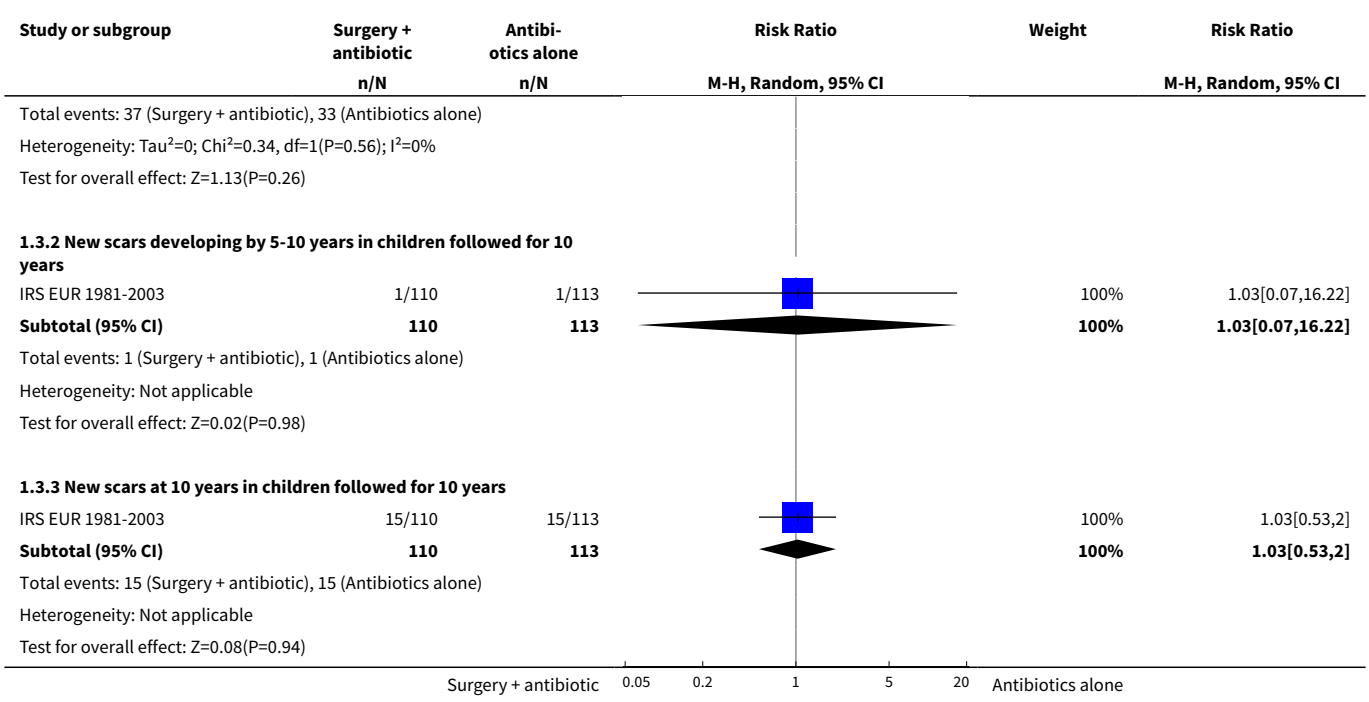
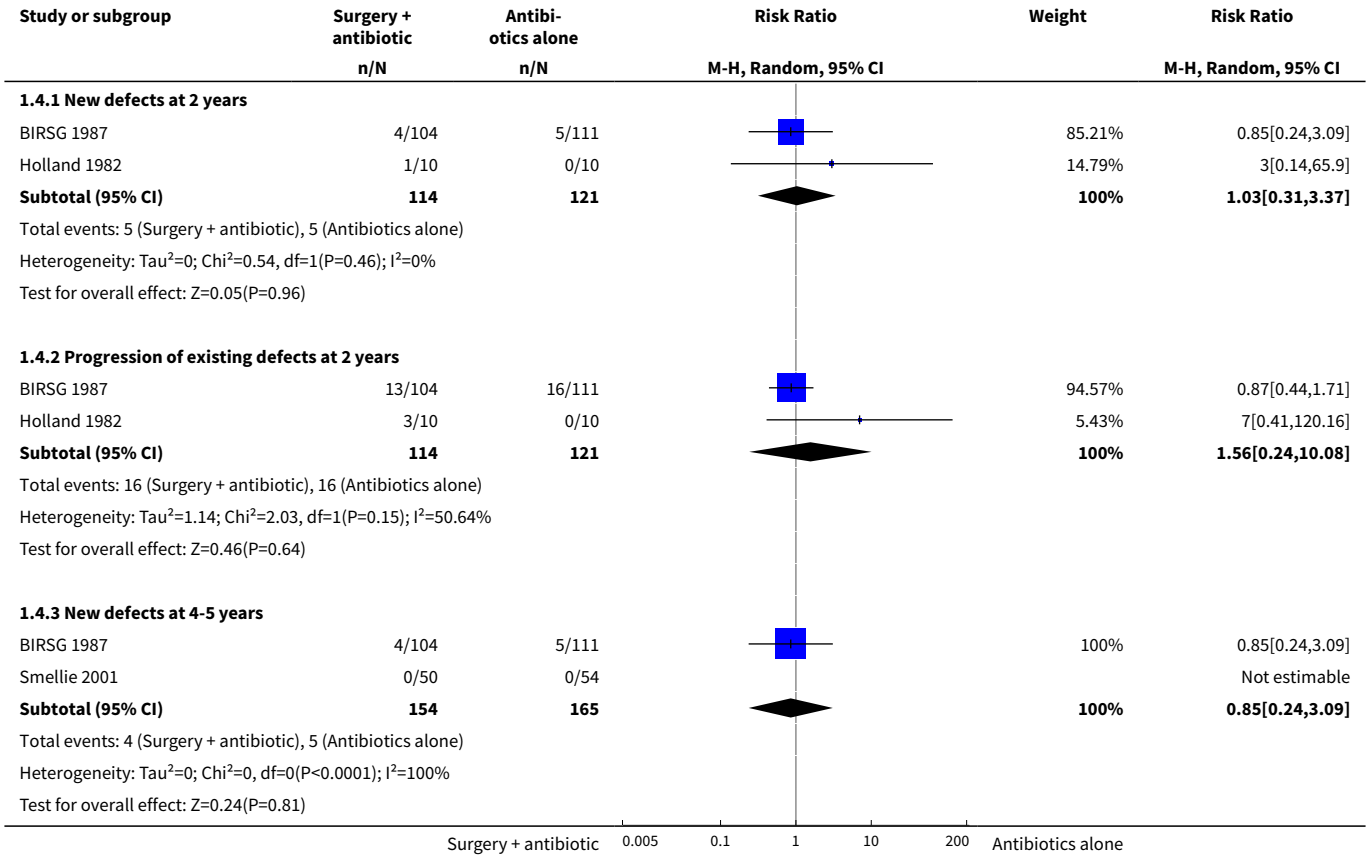


Analysis 1.4. Comparison 1 Reflux correction with surgery plus antibiotics (1-24 months) versus antibiotics alone, Outcome 4 Individual kidney data: Renal parenchymal defects on IVP.



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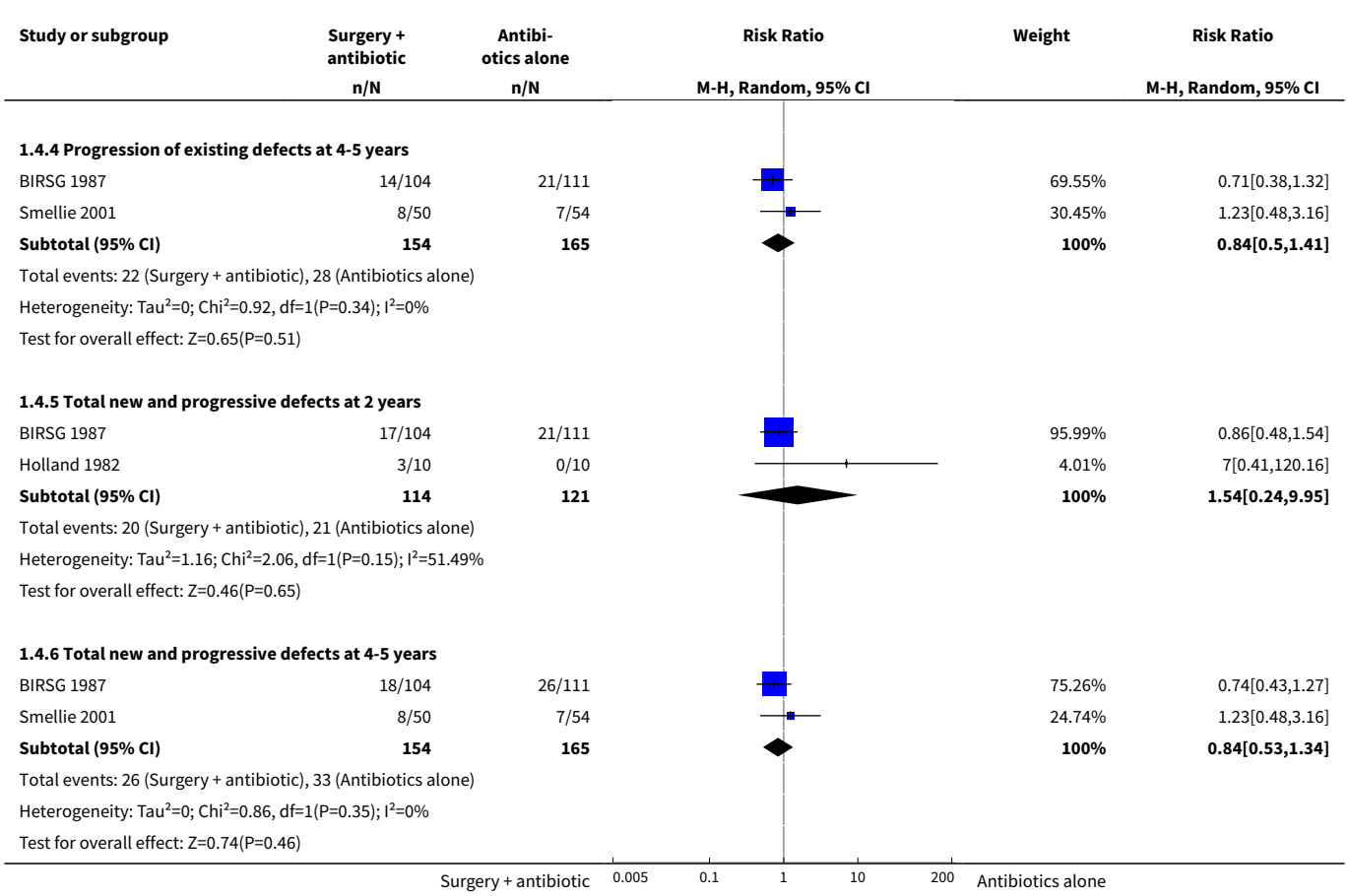
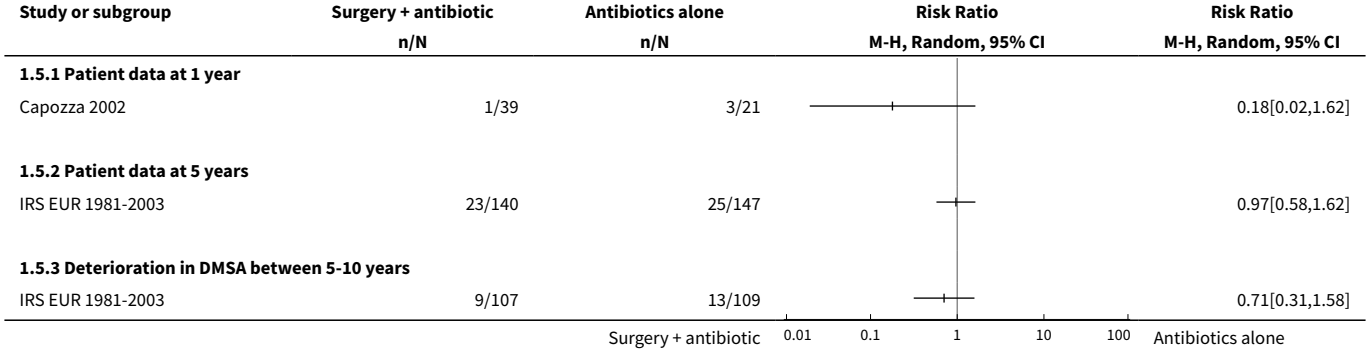


Analysis 1.5. Comparison 1 Reflux correction with surgery plus antibiotics (1-24 months) versus antibiotics alone, Outcome 5 Renal parenchymal defects on DMSA scintigraphy.



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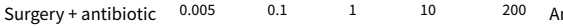
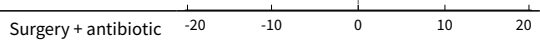
Analysis 1.6. Comparison 1 Reflux correction with surgery plus antibiotics (1-24 months) versus antibiotics alone, Outcome 6 Outcomes of hypertension and kidney failure.

Study or subgroup	Surgery + antibiotic n/N	Antibiotics alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 End-stage kidney failure					
BIRSG 1987	1/51	1/53		31.92%	1.04[0.07,16.18]
Smellie 2001	2/24	2/26		68.08%	1.08[0.17,7.1]
Subtotal (95% CI)	**75**	**79**		**100%**	**1.07[0.23,5.04]**
Total events: 3 (Surgery + antibiotic), 3 (Antibiotics alone)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.98); I^2=0%					
Test for overall effect: Z=0.08(P=0.93)					
1.6.2 Hypertension					
BIRSG 1987	1/51	3/53		27.99%	0.35[0.04,3.22]
Smellie 2001	4/24	3/26		72.01%	1.44[0.36,5.8]
Subtotal (95% CI)	**75**	**79**		**100%**	**0.93[0.25,3.42]**
Total events: 5 (Surgery + antibiotic), 6 (Antibiotics alone)					
Heterogeneity: Tau^2=0.14; Chi^2=1.15, df=1(P=0.28); I^2=13.34%					
Test for overall effect: Z=0.11(P=0.91)					
1.6.3 Hypertension at 10 years					
IRS EUR 1981-2003	0/125	3/127		100%	0.15[0.01,2.78]
Subtotal (95% CI)	**125**	**127**		**100%**	**0.15[0.01,2.78]**
Total events: 0 (Surgery + antibiotic), 3 (Antibiotics alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.28(P=0.2)					



Analysis 1.7. Comparison 1 Reflux correction with surgery plus antibiotics (1-24 months) versus antibiotics alone, Outcome 7 GFR measured by Schwartz formula.

Study or subgroup	Surgery + antibiotic N	Surgery + antibiotic Mean(SD)	Antibiotics N	Antibiotics Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.7.1 GFR at entry						
IRS EUR 1981-2003	126	105 (21)	132	106 (29)		-1[-7.16,5.16]
1.7.2 GFR at 5 years						
IRS EUR 1981-2003	141	117 (18)	144	115 (20)		2[-2.42,6.42]
1.7.3 GFR at 10 years						
IRS EUR 1981-2003	52	123 (33)	60	121 (23)		2[-8.69,12.69]



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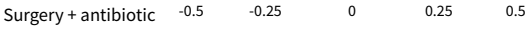
Analysis 1.8. Comparison 1 Reflux correction with surgery plus antibiotics (1-24 months) versus antibiotics alone, Outcome 8 Height SDS.

Study or subgroup	Surgery + antibiotic N	Surgery + antibiotic Mean(SD)	Antibiotics N	Antibiotics Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.8.1 Height Standard Deviation Score at entry						
IRS EUR 1981-2003	151	0.3 (1.4)	155	0.2 (1.4)		0.06[-0.25,0.37]
1.8.2 Height Standard Deviation Score at 10 year follow-up						
IRS EUR 1981-2003	118	0.2 (1.4)	118	0.1 (1.3)		0.09[-0.25,0.43]

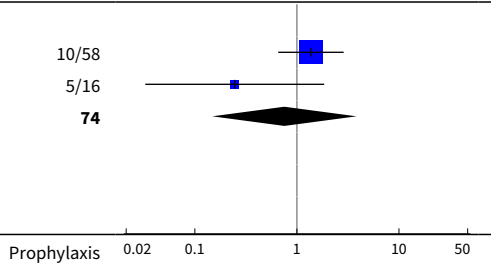


Comparison 2. Antibiotic prophylaxis versus surveillance/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All UTI	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Continuous antibiotics versus surveillance	2	142	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.15, 3.84]
1.2 Intermittent antibiotics versus surveillance	1	30	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.10, 2.00]
2 Febrile UTI	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Continuous antibiotics versus surveillance	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Renal parenchymal abnormalities	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Continuous antibiotics versus surveillance	2	142	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.36, 8.07]
3.2 Intermittent antibiotics versus surveillance	1	30	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.02, 8.59]

Analysis 2.1. Comparison 2 Antibiotic prophylaxis versus surveillance/no treatment, Outcome 1 All UTI.

Study or subgroup	Prophylaxis n/N	No prophylaxis n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Continuous antibiotics versus surveillance					
Garin 2006	13/55	10/58		73.08%	1.37[0.66,2.87]
Reddy 1997	1/13	5/16		26.92%	0.25[0.03,1.85]
Subtotal (95% CI)	**68**	**74**		**100%**	**0.75[0.15,3.84]**
Total events: 14 (Prophylaxis), 15 (No prophylaxis)					
Heterogeneity: Tau²=0.92; Chi²=2.53, df=1(P=0.11); I²=60.46%					
Test for overall effect: Z=0.34(P=0.73)					



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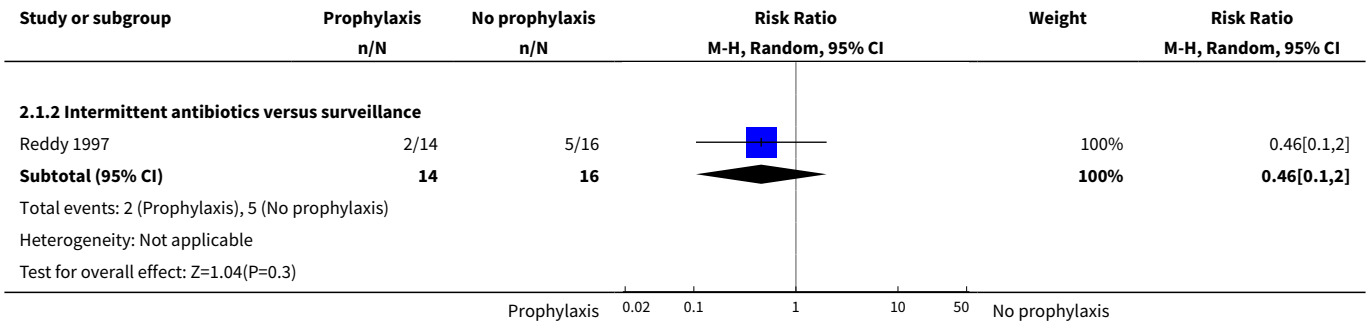
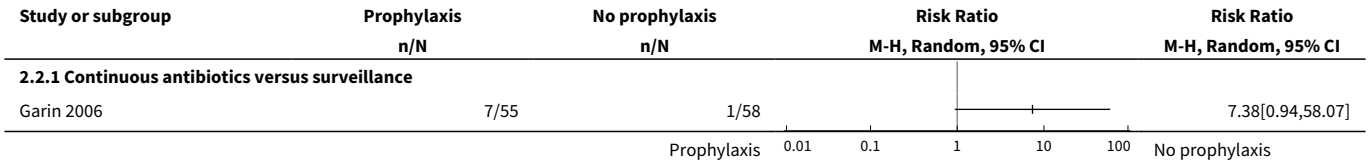
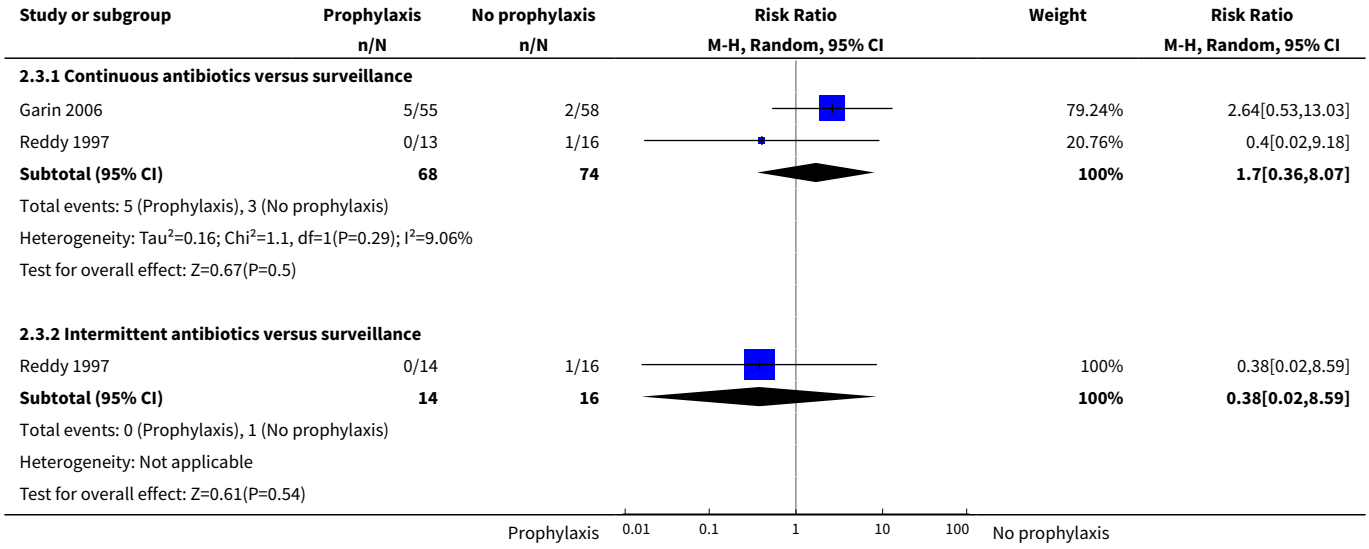


Analysis 2.2. Comparison 2 Antibiotic prophylaxis versus surveillance/no treatment, Outcome 2 Febrile UTI.



Analysis 2.3. Comparison 2 Antibiotic prophylaxis versus surveillance/ no treatment, Outcome 3 Renal parenchymal abnormalities.



Comparison 3. Different materials for subureteric injection to correct VUR

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Macroplastique versus Deflux	1		Risk Ratio (M-H, Random, 95% CI)	Totals not select-ed

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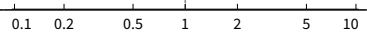
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Number of ureters with persistent VUR > grade 1 at 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Number of ureters with persistent VUR > grade 1 at 1 year	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Number of kidneys with temporary renal dilatation after injection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Number of children with UTI	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Collagen GAX 65 versus Collagen GAX 35	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Number of ureters with persistent VUR at 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Number of ureters with recurrence of VUR	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Different materials for subureteric injection to correct VUR, Outcome 1 Macroplastique versus Deflux.

Study or subgroup	Macroplastique n/N	Deflux n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.1.1 Number of ureters with persistent VUR > grade 1 at 3 months				
Oswald 2002	8/58	16/56		0.48[0.22,1.04]
3.1.2 Number of ureters with persistent VUR > grade 1 at 1 year				
Oswald 2002	8/41	10/32		0.62[0.28,1.4]
3.1.3 Number of kidneys with temporary renal dilatation after injection				
Oswald 2002	23/58	12/56		1.85[1.02,3.35]
3.1.4 Number of children with UTI				
Oswald 2002	6/34	4/38		1.68[0.52,5.44]



Analysis 3.2. Comparison 3 Different materials for subureteric injection to correct VUR, Outcome 2 Collagen GAX 65 versus Collagen GAX 35.

Study or subgroup	GAX 65 n/N	GAX 35 n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.2.1 Number of ureters with persistent VUR at 3 months				
Frey 1997	2/16	7/12		0.21[0.05,0.85]

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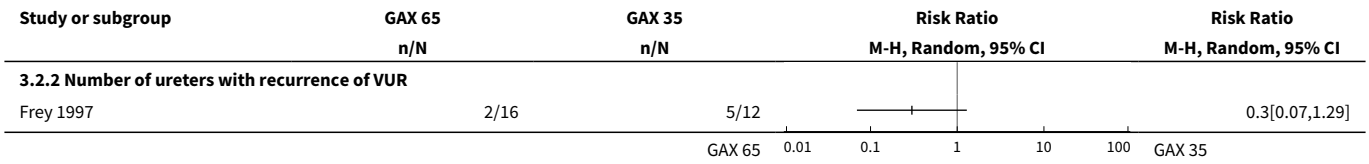

ADDITIONAL TABLES

Table 1. Quality of included studies

Study ID	Allocation concealment	Blinding - outcome assessors	UTI outcome	Loss to follow-up	ITT	Notes
BIRSG 1987	Sealed envelope	Radiological outcomes only	Frequency: 3 monthly Definition: 10(5)/mL Method of collection: NS	2 years: 14%	NS	
Capozza 2002	SAS software, blinded 2:1 randomisation	NS	Frequency of testing: clinic visits Definition: NS Method of collection: NS	1 year: 2%	No (1 excluded - no procedure performed)	8 patients with persistent reflux after implantation at 6 months withdrawn
Frey 1997	Unclear	NS	Not an outcome	3 months: 0%	NS	
Garin 2006	Unclear	NS	Frequency of testing: 3 monthly & at clinic visits	1 year: 9.2% of all 236 patients did not complete 1 year & excluded	No	Not clear whether excluded patients lost to follow-up
Holland 1982	Unclear	Radiological outcomes only	Frequency: daily dipstick test for nitrites, monthly culture Definition: NS Method of collection: clean catch	2 years: 0%	NS	10 non-randomised patients run in parallel
IRS EUR 1981-2003	Sealed envelope	NS	Frequency: "regular" home dipstick or health centre culture Definition: 10(5)/mL Method of collection: mid stream Febrile UTI: fever > 38.5C, abdominal or flank pain, fatigue	5 years: 11%	NS	7% incidence of postoperative obstruction
IRS USA 1992	Sealed envelope	NS	Frequency of testing: NS Definition: 10(5)/mL Method of collection: mid stream	5 years: 9%	No (15 who changed treatment	24 patients from antibiotic transferred to combined group by end of follow-up due to repeat UTI

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Table 1. Quality of included studies *(Continued)*

			Febrile UTI: fever > 38.5C, abdominal or flank pain, fatigue		status excluded)	
Morris 1991	Not stated	NS	Frequency: monthly urine culture Definition: NS Method of collection: NS	2 years: 10% 5 years: 42%	NS	Published in conference proceedings only DMSA scintigraphy performed but data not presented
Oswald 2002	Unclear	NS	Frequency of testing: NS Definition: NS	1 year: 0%	NS	
Reddy 1997	Unclear	NS	Frequency of testing: daily urine nitrate test except in continuous antibiotic group Definition: NS Method of collection: NS	I year: 0%	NS	Only continuous antibiotic and no treatment groups included in analysis.
Smellie 2001	Sealed envelope	NS	Frequency of testing: NS Definition: culture positive Method of collection: NS	4 years: 6% 10 years: 9%	No (1 withdrawn)	3 patients from antibiotic group had reimplantations

FEEDBACK

Grade of Reflux

Summary

It is difficult to accept the fact that Surgery does not help. There are specific indications for surgery especially in the realm of paediatric VUR. A more appropriate study would have been to compare the two groups (surgery vs conservative)in a similar grade of reflux and as such the controversy exists only in Gr3 reflux.

Regarding the assessment of children with UTI it is clear cut that the first investigation will be Ultrasound examination Followed by MCU.

Reply

Response to Dr Philipraj

This systematic review of randomised controlled trials has summarised the results of published and unpublished trials identified by a comprehensive search of literature sources. The majority of published trials have compared surgery and antibiotic prophylaxis with antibiotic prophylaxis. The large trials (Birmingham Reflux Study, International Reflux Study) only enrolled children with dilating reflux - equivalent to grade 3 or more on the International Classification. The International Reflux Study only enrolled children with grade 3 and 4 reflux; children with grade 5 reflux were excluded. There were no trials identified that compared surgery and antibiotic prophylaxis only and only enrolled children with grade 3 reflux. When data from these trials are combined in meta-analysis, there were no significant differences in the risk for further urinary tract infection or for renal scarring. In the International Reflux Study, the incidence of febrile urinary tract infections over 5 years of follow up was significantly reduced in children undergoing surgery compared with antibiotic prophylaxis. This was the only benefit of surgery over antibiotic prophylaxis that could be demonstrated. Otherwise the available trials have not demonstrated an additional benefit of surgery over antibiotic prophylaxis.

This systematic review of treatment cannot provide any information on the most appropriate investigations for children following urinary tract infection.

Contributors

Dr.S.Joseph Philipraj
Urologist
padisahana@yahoo.com
Dept of urology, Dr.T.M.A.Pai hospital, Kasturba Medical college, Udupi-576101, Karnataka,India.
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WHAT'S NEW

Date	Event	Description
13 May 2009	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 1999
Review first published: Issue 3, 2004

Date	Event	Description
9 October 2008	Amended	Converted to new review format.
15 May 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

- DW: Protocol development, study eligibility, data extraction, data analysis, writing review
- DV: Protocol development, study eligibility, data extraction
- EMH: Data extraction, data analysis, writing review
- GHS: Protocol development, data extraction, writing review
- JC: Protocol development, writing review

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Australian Kidney Foundation, Seeding Grant number S2/99, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibiotic Prophylaxis; Fever [etiology] [prevention & control]; Kidney [abnormalities]; Randomized Controlled Trials as Topic; Urinary Tract Infections [complications] [*prevention & control]; Vesico-Ureteral Reflux [complications] [*therapy]

MeSH check words

Child; Female; Humans; Male

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