Antibiotics and surgery for vesicoureteric reflux: a meta-analysis of randomised controlled trials

D Wheeler, D Vimalachandra, E M Hodson, L P Roy, G Smith, J C Craig

Aims: To evaluate the benefits and harms of treatments for vesicoureteric reflux in children.

Methods: Meta-analyses of randomised controlled trials using a random effects model. Main outcome measures were incidence of urinary tract infection (UTI), new or progressive renal damage, renal growth, hypertension, and glomerular filtration rate.

Results: Eight trials involving 859 evaluable children comparing long term antibiotics with surgical correction of reflux (VUR) and antibiotics (seven trials) and antibiotics compared with no treatment (one trial) were identified. Risk of UTI by 1–2 and 5 years was not significantly different between surgical and medical groups (relative risk (RR) by 2 years 1.07; 95% confidence interval (CI) 0.55 to 2.09, RR by 5 years 0.99; 95% CI 0.79 to 1.26). Combined treatment resulted in a 60% reduction in febrile UTI by 5 years (RR 0.43; 95% CI 0.27 to 0.70) but no concomitant significant reduction in risk of new or progressive renal damage at 5 years (RR 1.05; 95% CI 0.85 to 1.29). In one small study no significant differences in risk for UTI or renal damage were found between antibiotic prophylaxis and no treatment.

Conclusion: It is uncertain whether the identification and 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.

Original Article

Primary vesicoureteric reflux is thought to be caused by a maturational abnormality of the vesicoureteric junction, so that urine passes in a retrograde manner up the ureter. Although the exact prevalence in the general childhood population is unknown, about a third of children with urinary tract infection are consistently found to have reflux. Urinary tract infection occurs in approximately 5–10% of children, and so 1–3% of children are identified with vesicoureteric reflux.

It is believed that vesicoureteric reflux is a predisposing factor for urinary tract infection, which in turn may involve the kidney substance and cause permanent renal injury. Thus, the central management strategy for children with vesicoureteric reflux has been the avoidance of urinary tract infection induced damage. 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 periureteral injection of polytetrafluoroethylene, glutaraldehyde cross linked bovine collagen, dextranomer/hyaluronic acid copolymer, or polydimethylsiloxane have been trialled.

Little has been published about the harms of diagnosing and treating vesicoureteric reflux in children. The diagnosis of vesicoureteric reflux is usually made by a micturating cystourethrogram, an invasive test that requires urethral catheterisation and is frequently disturbing to children and their parents. It also carries the theoretical risks of iatrogenic urinary tract infection and radiation exposure. Surgical reimplantation has general risks of anaesthetic use, postoperative infection, and ureteric obstruction. There is increasing concern about the development of antibiotic resistant bacteria following long term antibiotic use. Quantifying these potential harms is problematic.

Although a common problem in childhood and frequently managed by clinicians, there is considerable disagreement regarding the best form of treatment for children with vesicoureteric reflux. We conducted a systematic review of randomised controlled trials (RCT) of the effects of interventions in patients with vesicoureteric reflux (VUR) on urinary tract infection (UTI) and renal parenchymal injury. The aims were to evaluate whether any intervention is better than no treatment and to evaluate the benefits and harms of the different treatment options currently utilised.

Methods

Inclusion criteria

We included randomised or quasi-randomised controlled trials, which evaluated the management of patients with primary VUR and included outcome data on UTI and/or renal parenchymal injury. The study subjects were patients of any age with VUR diagnosed by micturating cystourethrogram, but without any major urological or structural abnormalities such as obstructive uropathy or spina bifida. Any form of treatment of vesicoureteric reflux was analysed, including surgery (open and closed techniques), antibiotic prophylaxis, non-invasive techniques such as management of voiding dysfunction, and any combination of therapies. Treatment outcomes were collected according to predefined criteria, and included incidence of UTI, renal parenchymal abnormality, end stage renal disease, hypertension, renal functional impairment, and any adverse effects of treatment such as postoperative obstruction.

Literature search

Medline (1966 to February 2003) and Embase (1988 to February 2003) were searched independently by two reviewers (DV, DW).
A meta-analysis of vesicoureteric reflux (VUR) trials was conducted to evaluate the effectiveness of interventions for children with VUR. The study included 11 randomized controlled trials (RCTs) that compared various treatments with placebo or no treatment. The outcomes assessed included resolution of reflux, renal damage, urinary tract infection (UTI), and creatinine levels.

### Table 1: Characteristics of Trials of Interventions for Children with Vesicoureteric Reflux

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>No. enrolled/evaluated</th>
<th>Participants</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Duration of antibiotics</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holland (1992)</td>
<td>USA</td>
<td>10/10</td>
<td>Children 2 months – 10 years (mean 4.75 years)</td>
<td>Reflux grade II–IV, with normal renal function and blood pressure</td>
<td>Antibiotic: trimethoprim-sulphamethoxazole or nitrofurantoin 1 mg/kg Combined: reimplantation (not specified) and antibiotics</td>
<td>Both groups: 5 months – 16 months (mean 17 months)</td>
<td>• UTI – culture positive</td>
</tr>
<tr>
<td>BRS (1987)</td>
<td>UK</td>
<td>179/161</td>
<td>Children &lt;15 years</td>
<td>Reflux grade II with scarring or grade III, IV, V in absence of UTI within last 12 months</td>
<td>Antibiotic: trimethoprim or nitrofurantoin 1–2 mg/kg Combined: PL or Cohen reimplantation and antibiotics</td>
<td>Antibiotic: 2 years if resolution of reflux or 5 years Combined: 2 years</td>
<td>• UTI – culture positive</td>
</tr>
<tr>
<td>Morris (1991)</td>
<td>New Zealand</td>
<td>138/118</td>
<td>Children 6 months – 10 years</td>
<td>Reflux grade III–IV, no major urological abnormality</td>
<td>Antibiotic: type and dose not stated Combined: Cohen reimplantation and antibiotics</td>
<td>Antibiotic: 2 years Combined: 3 months</td>
<td>• UTI – culture positive</td>
</tr>
<tr>
<td>IRS Europe</td>
<td>Europe</td>
<td>321/302</td>
<td>Children 6 days – 11 years</td>
<td>Reflux grade III or IV, no previous urinary tract surgery, creatinine normal</td>
<td>Antibiotic: nitrofurantoin or trimethoprim 1–2 mg/kg Combined: PL, Cohen, LG reimplantation and antibiotics</td>
<td>Antibiotic: resolution of reflux or 5 years Combined: 6 months</td>
<td>• UTI – culture positive</td>
</tr>
<tr>
<td>IRS US</td>
<td>USA</td>
<td>142/132</td>
<td>Children &lt;10 years</td>
<td>Reflux grade III or IV, no major urological abnormality, no previous urinary tract surgery, creatinine normal</td>
<td>Antibiotic: nitrofurantoin or trimethoprim 1–2 mg/kg Combined: PL, Cohen, LG reimplantation and antibiotics</td>
<td>Antibiotic: resolution of reflux or 5 years Combined: 6 months</td>
<td>• UTI – culture positive</td>
</tr>
<tr>
<td>Reddy (1997)</td>
<td>USA</td>
<td>43/29</td>
<td>Children: age range not stated Source: university teaching hospitals</td>
<td>Reflux grade not stated, newly diagnosed</td>
<td>Antibiotic prophylaxis: antibiotic not specified No treatment: daily urine nitrate Intermitent antibiotics 3 times per wk</td>
<td>Antibiotic: 1 year</td>
<td>• UTI</td>
</tr>
<tr>
<td>Smellie (2001)</td>
<td>UK</td>
<td>53/50</td>
<td>Children 1–12 years</td>
<td>Reflux grade III–V with bilateral abnormal IVP, no major urological abnormality</td>
<td>Antibiotic: nitrofurantoin or trimethoprim or trimethoprim-sulphamethoxazole Combined: Cohen and antibiotics</td>
<td>Antibiotic: variable 6 months</td>
<td>• UTI – culture positive</td>
</tr>
<tr>
<td>Capozza (2002)</td>
<td>Italy</td>
<td>61/60</td>
<td>Children &gt; 1 year</td>
<td>Reflux grade II–IV for &gt; 6 mth, no major urological abnormality, no recurrent UTI</td>
<td>Antibiotic: Not specified Combined: Dx/HA copolymer implantation and antibiotics</td>
<td>Antibiotic: 1 year Combined: 1 month</td>
<td>• UTI</td>
</tr>
</tbody>
</table>

*Grade of reflux standardised to the International Reflux Study. †On intravenous pyelogram. ‡Glomerular filtration rate. §On renal ultrasound. 

Discrepancies were resolved by discussion with a fourth author (JC). Where the results of a study were published more than once or results were detailed in a number of publications, the most complete data was sought from all sources and included only once for each analysis.

For dichotomous outcomes the relative risks (RR) with 95% confidence intervals (CI) were calculated using Review Manager 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 effects model was also used to test the robustness of the analysis and for outliers. Heterogeneity between studies was analysed using Cochran’s Q statistic with an α of 0.1 used for statistical significance.

**RESULTS**

**Literature search**

Full paper assessment identified 11 RCTs. The International Reflux Study (IRS) was reported in two arms, European and US, and so has been treated as two separate studies. Three trials were subsequently excluded. Two trials compared different materials for subureteric implantation with resolution of...
reflux being the only outcome recorded. One trial was 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. Two included trials were identified by review of personal reference lists of the authors and have been published in conference proceedings only.

### Trial characteristics

Seven RCTs were identified (table 1) which compared the effectiveness of long term antibiotic administration with a combination of antibiotic prophylaxis for 1–24 months and ureteric reimplantation by open surgery (six trials) or Dx/HA copolymer subureteric implantation (one trial). An eighth trial compared no treatment with two antibiotic prophylaxis regimens (daily or intermittent antibiotic administration). The eight trials enrolled 947 children under the age of 15 years from the USA, Europe, and New Zealand; data for at least one outcome were available from 859 children. No RCT of any intervention in adults was found. No RCT was identified which compared antibiotics alone with surgery alone or used other interventions including manoeuvres for voiding dysfunction. A variety of open surgical techniques were used to correct vesicoureteric reflux, and trimethoprim, trimethoprim/sulphamethoxazole, or nitrofurantoin were used for antibiotic chemoprophylaxis. Generally only children with higher (dilating) grades of vesicoureteric reflux were included in the trials and outcomes were reported at 1–10 years post-randomisation.

### Trial quality

The method of treatment allocation was satisfactory in five trials (table 2). Only two trials reported that assessment of radiological outcomes was determined without knowledge of treatment groups. Intention to treat analysis was not performed in three trials; in the remaining trials 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: 0–2% at 1–2 years, and 9–42% at 4–10 years of follow up.

### Outcomes of trials comparing antibiotic prophylaxis with surgery and antibiotics

We combined the results of seven trials comparing antibiotic prophylaxis with combined surgery and antibiotics to obtain summary measures of treatment effects. There was no appreciable difference between the summary estimators using random and fixed effects models (data available on request). Only the results of the random effects models are reported here. The outcomes of urinary tract infection and renal parenchymal abnormality did not appear to be heterogeneous (figs 1 and 2), and formal testing for heterogeneity confirmed this. There were insufficient trials to explore potential effect modification using subgroup analysis or meta-regression.

### Urinary tract infection

Criteria for UTI, the primary outcome in most trials, were either not given or the microbiological threshold of >10³ colony forming units per ml was used. Symptomatic and asymptomatic UTI were not differentiated except in the International Reflux Study (both arms) 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 1–2 years and/or 4–5 years of follow up.

The frequency of all forms of recurrent UTI varied between 0% and 42% in the antibiotic only group, and between 20%...
and 22% in the combined treatment group by 2 years of follow up (fig 1). By 2 years, there was no significant reduction in the risk of urinary tract infection in the combined treatment group compared with the antibiotic only group (four trials; relative risk (RR) 1.07; 95% confidence interval (CI) 0.55 to 2.09). By 5 years the frequency of all forms of recurrent UTI was 29–42% in the antibiotic only group and 25–40% in the combined treatment group. By five years, there was no significant difference in the risk of UTI between groups (three trials; RR 0.99; 95% CI 0.79 to 1.26). 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 8–10% in the combined therapy groups by 5 years of follow up (fig 1). Children in the combined treatment group had fewer febrile UTI than the antibiotic alone group by 5 years (two trials; RR 0.43; 95% CI 0.27 to 0.70). 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 (1 trial; RR 0.96; 95% CI 0.67 to 1.39). This occurred because the increased risk of febrile infections in the antibiotic only group was matched by a similar reduction in risk of afebrile symptomatic infections in the antibiotic only group compared with the combined treatment group.

Renal parenchymal abnormality

New and progressive renal parenchymal abnormality on intravenous pyelography were the primary radiological outcomes reported by five trials. No significant differences were found for the risks for new (two trials; RR 1.06; 95% CI 0.33 to 3.42) or progressive renal parenchymal defects (two trials; RR 1.62; 95% CI 0.25 to 10.48) between the treatment groups at 2 years of follow up (fig 2). Similarly the risks for new (four trials; RR 1.06; 95% CI 0.77 to 1.45) or progressive renal parenchymal defects (three trials; RR 0.97; 95% CI 0.67 to 1.40) were not significantly different at 4–5 years of follow up (fig 2).

The European arm of the International Reflux Study also ascertained renal parenchymal abnormality at 5 years using "Tm-dimercaptosuccinic acid scintigraphy." Approximately 90% (287/321) of randomised children had scintigraphy performed. Relative to the antibiotic only group, there was a small (5%) but non-significant increased risk of new or progressive scan abnormalities in the combined treatment group (one trial; RR 1.05; 95% CI 0.62 to 1.77, 18% versus 16%).

Renal growth was evaluated in four studies21 26 34 36 at 2–10 years by measurements of changes in renal length standard deviation scores (three trials; 510 children) or renal area (one study; 82 children) on intravenous pyelogram (table 1). No significant differences between groups were found at any time point or in any age group. Combining 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, end stage renal failure and hypertension, were reported by the two UK studies. In total six children developed end stage renal failure (three in each arm), and eight children developed hypertension (five in the antibiotic only arm and three in the combined treatment arm). Four studies25 28 29 30 reported data on glomerular filtration rates, 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.

Resolution of reflux was an outcome described in six studies, but combining of individual trial data was not possible because of differences in reporting practices (patients and ureters), not all patients having follow up micturating cystourethrograms and missing data. In four trials20 21 22 36 the postoperative resolution rate at 4–5 years for ureters was 93–99%. Over the same follow up period, between 16% and 49% of patients had spontaneous resolution of vesicoureteric reflux.21 22 28 30 31 36 The resolution rate at 12 months for patients after Dx/HA copolymer subureteric implantation was 69% compared with 38% in the antibiotics only group.5
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.

Outcomes of the trial comparing antibiotic prophylaxis with no treatment

In a single study,18 children were randomised to receive no treatment, daily antibiotic prophylaxis, or prophylaxis given on three days each week. There was no significant difference in risk for UTI (29 children; RR 0.25; 95% CI 0.03 to 1.85) or renal parenchymal injury (29 children; RR 0.40; 95% CI 0.02 to 9.18) between children given no therapy and children given daily antibiotics. No data on adverse events 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 trials with 833 evaluable patients comparing antibiotic prophylaxis with combined surgery and antibiotics. A single study involving 29 children found no difference in the risk for UTI or renal parenchymal injury between groups treated with antibiotic prophylaxis or no therapy. However, in the latter study small patient numbers resulted in wide confidence intervals so that differences between groups cannot be excluded.

The combined evidence from available randomised controlled trials of interventions in children with vesicoureteric reflux does not provide compelling reasons why the current practice of diagnosing and treating children with vesicoureteric reflux confers important health benefits. The diagnosis of vesicoureteric reflux is most commonly made after urinary tract infection in childhood, when it is widely recommended that children be investigated. With about a 5–10% cumulative incidence of urinary tract infection during childhood, many children have micturating cystourethrography. This test generally requires urethral catheterisation, which is distressing for the children and their families, involves exposure to ionising radiation, and may cause urinary tract infection. Medical intervention requires the use of long-term antibiotics, which may contribute to the global problem of the development of antibiotic resistant bacteria. The diagnosis of vesicoureteric reflux 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 urinary tract infection, renal “scarring”, hypertension, and chronic renal failure. These risks have been regarded as acceptable since the 1960s when the association was made between vesicoureteric reflux and renal parenchymal damage. Although there are associations between vesicoureteric reflux, urinary tract infection, and kidney damage, the assumption that vesicoureteric reflux...
is a modifiable risk factor is not based on strong empiric evidence from existing randomised controlled trials. In addition, recent data from prospective cohort studies suggest that in approximately 50% of children, renal parenchymal abnormalities reflect renal dysplasia associated with dilating VUR rather than damage caused by UTI. The belief that children with vesicoureteric reflux should be treated with surgery, antibiotics, or both developed in the 1960s from animal data which showed that infection in the presence of vesicoureteric reflux caused kidney damage. This belief still needs appropriate evaluation with a placebo controlled trial in children with vesicoureteric reflux to determine whether any therapy is effective in preventing significant and progressive renal injury.

If vesicoureteric reflux were an important modifiable risk factor for the development of urinary tract infection and renal parenchymal damage, we would anticipate a significant reduction in these outcomes for the combined surgical and antibiotic group relative to the antibiotic only group. Instead, there was no significant difference in the risk of urinary tract infection by 2 or 5 years, and no significant reduction in the risk of new or progressive areas of kidney damage at 5 years using intravenous pyelography or DMSA scintigraphy. Combined surgical and medical treatment only reduced the risk of febrile urinary tract infection at 5 years. Assuming a constant relative risk, the number of children requiring a reimplantation operation at different baseline risk of recurrent infection can be calculated. If the risk were 20%, about nine children would need to be treated with combined reimplantation surgery and antibiotics compared with antibiotics alone to prevent one febrile UTI. If the risk were 10%, 17 children would need to be treated with combined surgical and medical therapy to prevent one febrile UTI. Of all the outcomes assessed, febrile urinary tract infection is the most subjective outcome and is liable to differential misclassification. If this were true of pyelonephritis we would expect to see a reduction in the incidence of new renal parenchymal defects, but this is not the case. A randomised comparison between surgical treatment and antibiotic treatment has not been performed; only trials 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.

In summary, our systematic review of randomised controlled trials of interventions for children with vesicoureteric reflux has identified a number of important and unanswered questions. Most importantly, it is not clear whether any intervention for children with primary vesicoureteric reflux 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 urinary tract infection and renal parenchymal abnormality. Furthermore, the trials, which have been undertaken comparing surgery and antibiotics with antibiotics alone, have shown any additional benefit of surgery except for a reduction in risk of febrile urinary tract infections. Well designed and adequately powered placebo controlled randomised trials of antibiotics alone in children with vesicoureteric reflux are now required. 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 as they consider how best to investigate children following urinary tract infection and treat those with vesicoureteric reflux.

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REFERENCES


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Origins of peanut allergy

“I call a spade a spade.”

The use of straightforward language could prevent a lot of trouble. It seems bizarre, for instance, that when we use peanut oil medically we call it arachis oil so that many doctors and nurses, and almost all of the general public, must be unaware of what it is. Much has been written about the apparent increase in peanut allergy in recent decades but there is still a good deal of uncertainty about its origins. Now data from the Avon Longitudinal Study of Parents and Children (Gideon Lack and colleagues. *New England Journal of Medicine* 2003;348:977–85) have pointed to the use of peanut oil skin preparations in young children as a possibly important factor.

From a cohort of 13,971 pre-school children born between April 1991 and December 1992, 49 were found to have a convincing history of peanut allergy. Thirty-six of these had skin testing and double blind, placebo controlled oral peanut challenge testing. Twenty-nine had positive skin reactions to peanut and 23 of those had positive challenge tests. The 49 children were compared with 70 atopic (eczema in mother and child) controls and 140 normal controls.

Specific IgE to peanuts was not detectable in saved cord blood from 23 children with peanut allergy and there was no significant correlation between peanut allergy and maternal peanut consumption in pregnancy. Transplacental sensitisation of the fetus therefore seemed unlikely. Likewise, sensitisation through breastfeeding was unlikely because peanut allergy was not significantly related to breastfeeding or to maternal peanut consumption during lactation; neither was there an association with the use of breast creams containing peanut oil.

Peanut allergy was, however, significantly associated with having been given soy milk or soy formula in the first 2 years of life and with eczematous rashes in infancy. The effect of soy could not be explained simply on the grounds of its use for allergic manifestations prior to the onset of peanut allergy. It is possible, but not proved, that cross-reacting allergens in soybeans might sensitise young children to peanuts.

Creams containing peanut oil were used very commonly for young infants: 59% of normal controls, 53% of atopic controls, 84% of children who developed peanut allergy, and 91% of children with a positive challenge test. They had been used as emollients for nappy rashes, eczema, dry skin, and other skin problems. The association with peanut allergy was not explained simply by the prevalence of skin problems in children who developed peanut allergy since children in the atopic control group were just as prone to skin problems but less likely to have had peanut oil creams applied. Creams not containing peanut oil had been used equally in the atopic control and peanut allergy groups. These researchers postulate that sensitisation occurs when peanut oil is applied to inflamed skin. The use of peanut oil cream increased the likelihood of peanut allergy sevenfold.

The use of peanut oil based emollient creams for young children is associated with increased risk of later peanut allergy. Soy milks might also increase the risk. At a time when there is so much anxiety about peanut allergy it seems strange, to put it mildly, that we are so busily applying peanut oil to the skin of young children. The mothers in this study did not know they were using peanut oil creams. Perhaps calling peanut oil peanut oil would be a good start.

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