

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

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*Arch Dis Child* 2003;**88**:688–694

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Accepted 11 March 2003

**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.

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.<sup>1</sup> Urinary tract infection occurs in approximately 5–10% of children, and so 1–3% of children are identified with vesicoureteric reflux.<sup>2</sup>

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.<sup>3</sup> 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.<sup>4–6</sup>

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.<sup>7</sup> 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.<sup>8</sup> There is increasing concern about the development of antibiotic resistant bacteria following long term antibiotic use.<sup>9</sup> 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.<sup>8</sup> 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,

**Abbreviations:** RCT, randomised controlled trial; UTI, urinary tract infection; VUR, vesicoureteric reflux

**Table 1** Characteristics of trials of interventions for children with vesicoureteric reflux

Study	Country	No. enrolled/ no. evaluated	Participants	Inclusion criteria	Intervention	Duration of antibiotics	Outcomes
Holland (1982) <sup>20</sup>	USA	10/10	Children 2 months – 10 years (mean 4.75 years) Source: not stated	Reflux grade* II–IV, with normal renal function and blood pressure	Antibiotic: trimethoprim-sulphamethoxazole or nitrofurantoin 1 mg/kg Combined: reimplantation (not specified) and antibiotics	Both groups: 5 month – 36 months (mean 17 months)	<ul style="list-style-type: none"> <li>• UTI – culture positive</li> <li>• Renal damage†</li> <li>• Adverse effects of antibiotics</li> </ul>
BRS (1987) <sup>21–23</sup>	UK	179/161	Children <15 years Source: GP, paediatrician referrals, hospital casualty	Reflux grade II with scarring or grade III, IV, V in absence of UTI within last 12 months	Antibiotic: trimethoprim or nitrofurantoin 1–2 mg/kg Combined: PL or Cohen reimplantation and antibiotics	Antibiotic: 2 year if resolution of reflux or 5 years Combined: 2 years	<ul style="list-style-type: none"> <li>• UTI – culture positive</li> <li>• Renal damage†</li> <li>• GFR‡</li> <li>• Resolution of reflux</li> <li>• Renal length</li> </ul>
Morris (1991) <sup>19</sup>	New Zealand	138/118	Children 6 months – 10 years Source: not stated	Reflux grade III–IV, no major urological abnormality	Antibiotic: type and dose not stated Combined: Cohen reimplantation and antibiotics	Antibiotic: 2 years Combined: 3 months	<ul style="list-style-type: none"> <li>• UTI – culture positive</li> <li>• GFR</li> <li>• Resolution of reflux</li> </ul>
IRS Europe (1992) <sup>15,24–32</sup>	Europe	321/302	Children 6 days – 11 years Source: university teaching hospitals	Reflux grade III or IV, no major urinary tract abnormality, no previous urinary tract surgery, creatinine normal	Antibiotic: nitrofurantoin or trimethoprim 1–2 mg/kg Combined: PL, Cohen, LG reimplantation and antibiotics	Antibiotic: resolution of reflux or 5 years Combined: 6 months	<ul style="list-style-type: none"> <li>• UTI – culture positive</li> <li>• Renal damage†</li> <li>• Obstruction post-op</li> <li>• Resolution of reflux</li> <li>• Renal length</li> </ul>
IRS US (1992) <sup>33–35</sup>	USA	142/132	Children <10 years Source: university teaching hospitals	Reflux grade III or IV, no major urinary tract abnormality, no previous urinary tract surgery, creatinine normal	Antibiotic: nitrofurantoin or trimethoprim 1–2 mg/kg Combined: PL, Cohen, or other reimplantation and antibiotics	Antibiotic: resolution of reflux or 5 years Combined: 6 months	<ul style="list-style-type: none"> <li>• UTI – culture positive</li> <li>• Renal damage†</li> <li>• Resolution of reflux</li> <li>• Renal area</li> </ul>
Reddy (1997) <sup>18</sup>	USA	43/29	Children: age range not stated Source: university teaching hospital	Reflux grade not stated, newly diagnosed	Antibiotic prophylaxis: antibiotic not specified No treatment: daily urine nitrate Intermittent antibiotics 3 times per wk	Antibiotic: 1 year	<ul style="list-style-type: none"> <li>• UTI</li> <li>• Renal damage¶</li> <li>• Resolution of reflux</li> </ul>
Smellie (2001) <sup>36</sup>	UK	53/50	Children 1–12 years Source: university teaching hospitals	Reflux grade III–V with bilateral abnormal IVP, no major urological abnormality	Antibiotic: nitrofurantoin or trimethoprim or trimethoprim-sulphamethoxazole 1–2 mg/kg Combined: Cohen and antibiotics	Antibiotic: variable Combined: 6 months	<ul style="list-style-type: none"> <li>• UTI – culture positive</li> <li>• Renal damage†</li> <li>• GFR (change)</li> <li>• Renal length (change)</li> </ul>
Capozza (2002) <sup>5</sup>	Italy	61/60	Children > 1 year Source: university teaching hospital	Reflux grade II–IV for ≥6 mth, no major urological abnormality, no recurrent UTI	Antibiotic: Not specified Combined: Dx/HA copolymer implantation and antibiotics	Antibiotic: 1 year Combined: 1 month	<ul style="list-style-type: none"> <li>• UTI</li> <li>• Renal damage§¶</li> <li>• GFR (change)</li> <li>• Resolution of reflux</li> </ul>

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

¶On 99m-technetium dimercaptosuccinic acid scan.

PL, Politano-Leadbetter procedure; LG, Lich-Gregoir procedure; Dx/HA copolymer, dextranomer/hyaluronic acid copolymer.

DW) without age or language restriction. The optimally sensitive search strategy for trials developed for the Cochrane Collaboration<sup>10,11</sup> was combined with medical subject headings and textwords specific for vesicoureteric reflux. The Cochrane Controlled Trials Register was searched in advanced search mode to identify any additional trials. Reference lists of retrieved articles were searched and those known to have conducted trials of treatment for vesicoureteric reflux were contacted.

### Data extraction and analysis

Relevant abstracts were reviewed independently by two authors (DV, DW) to determine suitability of inclusion. Any disagreements were resolved by discussion with a third author (JC). Where suitability was uncertain or no abstract available, the full article was obtained. Authors were contacted to obtain missing data where necessary.

Data extraction was conducted independently by three reviewers (DV, DW, GS) using a standardised checklist for outcomes and quality. The methodological quality of RCTs was evaluated based on randomisation method, allocation concealment, standardisation and blinding of outcome assessment, intention to treat analysis, and losses to follow up.<sup>12</sup> Any

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<sup>13</sup> 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  $\alpha$  of 0.1 used for statistical significance.<sup>14</sup>

## RESULTS

### Literature search

Full paper assessment identified 11 RCTs. The International Reflux Study<sup>15</sup> 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

**Table 2** Quality of included trials of interventions for children with vesicoureteric reflux

Study	Method of treatment allocation	Blinding of outcomes assessment	UTI outcome measurement (frequency, definitions, method of urine collection)	Loss to follow up (%)	Intention to treat	Notes
Holland (1982) <sup>20</sup>	Not stated	Radiological outcomes only	Frequency: daily dipstick test for nitrites, monthly culture Definition: not stated Method of collection: clean catch	2 years: 0%	Not stated	10 non-randomised patients run in parallel
BRS (1987) <sup>21-23</sup>	Sealed envelope	Radiological outcomes only	Frequency: 3 monthly Definition: 10 <sup>5</sup> /ml Method of collection: not stated	2 years: 14%	Not stated	
Morris (1991) <sup>19</sup>	Not stated	Not stated	Frequency: monthly urine culture Definition: not stated Method of collection: not stated	2 years: 10% 5 years: 42%	Not stated	Published in conference proceedings only DMSA scans performed but data not presented 7% incidence of postoperative obstruction
IRS Europe (1992) <sup>15 24-32</sup>	Sealed envelope	Not stated	Frequency: "regular" home dipstick or health centre culture Definition: 10 <sup>5</sup> /ml Method of collection: mid stream Febrile UTI: fever >38.5°C, abdominal or flank pain, fatigue	5 years: 11%	Not stated	
IRS US (1992) <sup>33-35</sup>	Sealed envelope	Not stated	Frequency of testing not stated Definition: 10 <sup>5</sup> /ml, method of collection: mid stream Febrile UTI: fever >38.5°C, abdominal or flank pain, fatigue	5 years: 9%	No (15 who changed treatment status excluded)	24 patients from antibiotic transferred to combined group by end of follow up due to repeat UTI
Reddy (1997) <sup>18</sup>	Not stated	Not stated	Frequency of testing: daily urine nitrate test except in continuous antibiotic group Definition: not stated Method of collection: not stated	1 year: 0%	Not stated	Only continuous antibiotic and no treatment groups included in analysis.
Smellie (2001) <sup>36</sup>	Sealed envelope	Not stated	Frequency of testing: not stated Definition: culture positive Method of collection: not stated	4 years: 6% 10 years: 9%	No (1 withdrawn)	3 patients from antibiotic group had reimplantations
Capozza (2002) <sup>5</sup>	SAS software, blinded, 2:1 randomisation	Not stated	Frequency of testing: clinic visits Definition: not stated Method of collection: not stated	1 year: 2%	No (1 excluded—no procedure performed)	8 patients with persistent reflux after implantation at 6 months withdrawn. Data on renal scarring for kidneys not patients

reflux being the only outcome recorded.<sup>6, 16</sup> 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.<sup>17</sup> Two included trials were identified by review of personal reference lists of the authors and have been published in conference proceedings only.<sup>18, 19</sup>

### 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<sup>18</sup> 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 managements 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

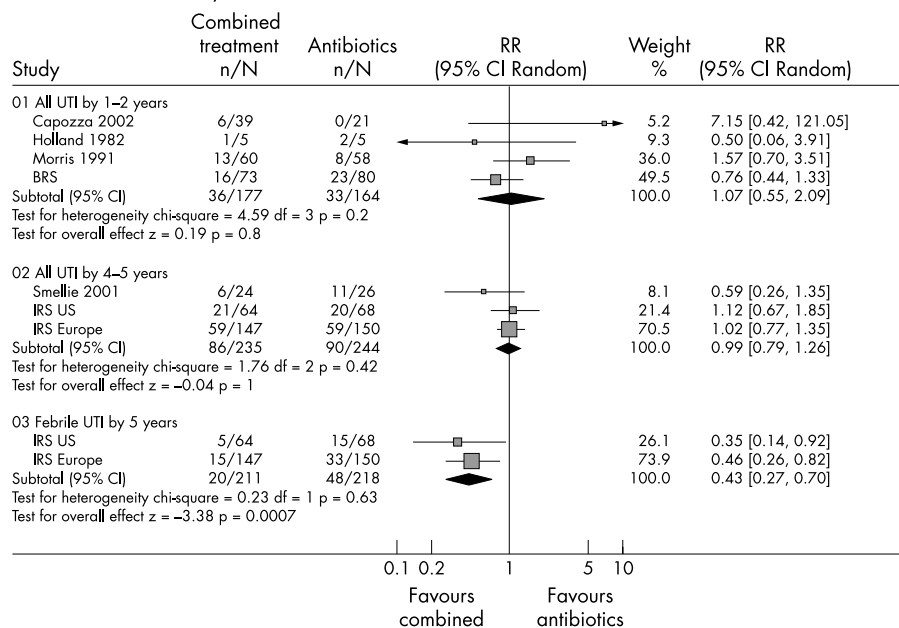
We combined the results of seven trials comparing antibiotic prophylaxis with combined surgery and antibiotics to obtain summary measures of treatment effects. There was no appreciable difference between the summary estimators using random and fixed effects models (data available on request). Only the 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 >10<sup>7</sup> 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%

Comparison: 01 combined reflux correction and antibiotics versus antibiotics alone  
 Outcome: 01 urinary tract infection



**Figure 1** Meta-analyses of relative risk (random effects model) of urinary tract infections. Subtotals pertain to all urinary tract infections at 2 years post-entry (outcome 01), all urinary tract infections at 5 years post-entry (outcome 02), and symptomatic (febrile) urinary tract infections at 5 years post-entry (outcome 03). BRS, Birmingham Reflux Study; IRS Europe, European arm of the International Reflux Study; IRS US, United States arm of the International Reflux Study. Trials are shown ordered by study weights. No heterogeneity was shown using Cochran's Q statistic ( $\chi^2$  analysis with degrees of freedom,  $df$ ). The test statistics Z indicate that there were no significant differences between the combined treatment group and the antibiotic only group of patients with vesicoureteric reflux except for febrile urinary tract infection (outcome 03).

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 (one 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

<sup>99m</sup>Tm-dimercaptosuccinic acid scintigraphy.<sup>31</sup> 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%).

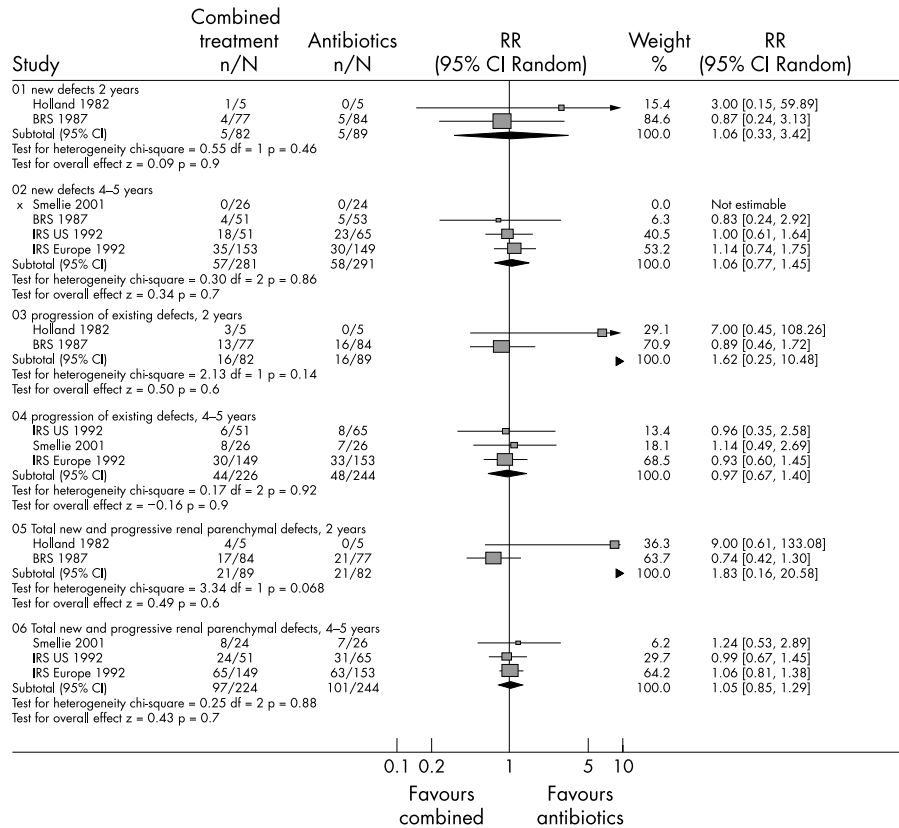
Renal growth was evaluated in four studies<sup>21 32 34 36</sup> at 2–10 years by measurements of changes in renal length standard deviation scores (three trials; 510 children) or renal area (one study; 82 children) on intravenous pyelogram (table 1). No significant differences between groups were found at any time point or in any age group. Combining 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, end stage renal failure and hypertension, were reported by the two UK studies.<sup>21 36</sup> 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 studies<sup>5 19 21 36</sup> 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 trials<sup>21 25 33 36</sup> 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.<sup>21 26 34 36</sup> The resolution rate at 12 months for patients after Dx/HA copolymer subureteric implantation was 69% compared with 38% in the antibiotics only group.<sup>5</sup>

Comparison: 01 combined surgery and antibiotics versus antibiotics alone  
 Outcome: 02 renal parenchymal defects



**Figure 2** Meta-analyses of relative risk (random effects model) for the development of renal parenchymal abnormalities diagnosed by intravenous pyelogram. Subtotals pertain to new defects at 2 and 5 years (outcomes 01 and 03), progression of those previously identified at 2 and 5 years post-entry (outcomes 02 and 04), and all defects, both new and progressive, at both 2 and 5 years (outcomes 05 and 06). BRS, Birmingham Reflux Study; IRS Europe, European arm of the International Reflux Study; IRS US, United States arm of the International Reflux Study. Trials are shown ordered by study weights. No heterogeneity was shown using Cochran's Q statistic ( $\chi^2$  analysis with degrees of freedom, df). The test statistics Z indicate that there were no significant differences between the combined treatment group and the antibiotic only group of patients with vesicoureteric reflux.

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,<sup>18</sup> 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,<sup>7</sup> 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.<sup>9</sup> 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.<sup>37</sup> 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 not 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.

#### ACKNOWLEDGEMENTS

The authors would like to thank Professor Les Irwig for his help with methodology and manuscript preparation, and those authors and experts in the field who replied to our requests for study information. This systematic review was performed under the auspices of the Cochrane Renal Group of the Cochrane Collaboration. This study was

funded in part by a seeding grant from the Australian Kidney Foundation (Grant no. S2/99).

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## ARCHIVIST .....

### Origins of peanut allergy

“I call a spade a spade.”

Robert Burton. *The Anatomy of Melancholy* (1621–51)

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.