Vesicoureteric reflux in children

Kjell Tullus

Vesicoureteric reflux is defined as the retrograde passage of urine from the bladder into one or both ureters and often up to the kidneys, and mainly affects babies and infants. In severe cases dilatation of the ureter, renal pelvis, and calyces might be seen. Traditionally it was thought that only a low percentage of children have vesicoureteric reflux, but studies have suggested as many as 25–40% are affected. Guidelines recommend that the number of investigations for vesicoureteric reflux in children who have had a febrile urinary tract infection be reduced, but this approach is controversial. The recommendations also suggest that prophylactic antibiotics and surgery should be avoided in children with non-severe vesicoureteric reflux. In this Seminar I present data on the management of children with vesicoureteric reflux and give suggestions on how to navigate this difficult area.

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Introduction

Vesicoureteric reflux in children has been viewed for several decades as an important risk factor for febrile urinary tract infections and postinfection scarring.[1,2] Guidelines on the management of urinary tract infections, however, downplay the importance of isolated vesicoureteric reflux. The guidelines from the UK National Institute for Health and Care Excellence and the American Academy of Pediatrics no longer recommend radiological investigations to detect vesicoureteric reflux in most children with uncomplicated febrile urinary tract infections. Both guidelines outline selected cases in which such investigations might be considered.[3,4]

Worldwide there is a trend towards reducing the number of investigations for vesicoureteric reflux. The number of investigations with invasive imaging of the urinary tract (micturition urethrocystogram [MCUG], nuclear medicine studies, and intravenous pyelography) was reduced in children in Australia from 11 169 in 1997–98, to 3361 10 years later.[5] In the USA, the hospital at which a child is treated is the most important factor in determining the therapeutic procedure he or she undergoes. The probability of a child undergoing endoscopic correction of vesicoureteric reflux varies from 7% to 85% dependent on the institution.[6] In this Seminar I summarise the information on the assessment and treatment of vesicoureteric reflux and assess the main gaps in knowledge.

Epidemiology

Vesicoureteric reflux is defined as the back flow of urine from the urinary bladder into one or both ureters, the renal pelvises, or both. Severity is graded in different ways. A widely used system is the International Reflux Study in Children, in which grade I indicates reflux of urine into part of the ureter and grade V indicates gross dilatation and tortuosity of the ureter, renal pelvis, and calyces, and the papillary impressions are no longer visible in most calyces (figure 1). Each ureter is graded separately and classification is usually based on the worse side.[7]

Vesicoureteric reflux has traditionally been viewed as an uncommon disorder that affects only a low percentage of all children (around 1%).[8] This notion, however, was based on studies from as early as 1916,[9] and has been challenged with suggestions that vesicoureteric reflux is notably more common and can affect healthy children.[10] MCUG data from 102 urologically normal infants and children from 1967 showed that as many as 65% of the infants displayed reflux in the first 6 months of life.[11] The rate gradually decreased until at the age of 5 years none of the investigated children showed vesicoureteric reflux.

For ethical reasons it is highly unlikely that further studies with MCUG will be done in healthy children. A Finnish group, however, retrospectively scrutinised diagnoses in a large cohort of children who had undergone MCUG because of presumed urinary tract infections. Data from 406 children were included and, on the basis of the presence of leucocytes and growth of bacteria in the urine at the time of assessment, were classified as certain (leucocyturia and substantial bacterial growth), possible, and improbable (no leucocytes in the urine and no growth or more than one uropathogen on the urine culture) urinary tract infection.[12] The proportion of children with vesicoureteric reflux was similar in all three groups: 36%, 28%, and 36%. The same group published findings for a further 2036 children with urinary tract infections retrospectively defined as proven, likely, unlikely, false, or having no microbial data.[13] The proportion of children with any vesicoureteric reflux was between 35% and 40%, and with high-grade vesicoureteric reflux was between 15% and 20% in all five groups. Williams and colleagues,[14] in Australia, estimated that the prevalence of vesicoureteric reflux was between 10% and 20%. A meta-analysis of several studies in which siblings were screened for vesicoureteric reflux showed prevalence of 27·4% (95% CI 2·9–51·9).[15]

Small-animal studies are not relevant when studying vesicoureteric reflux as, for example, 100% of rats have the disorder. Useful data are available from larger animals, such as infant macaque monkeys, in which mild to moderate vesicoureteric reflux was seen in 100% at age 3 months but only 20% by age 2 years.[16]

Although controversial, the case for prevalence of 25–40% in small children seems more compelling than the very low percentage purported previously.

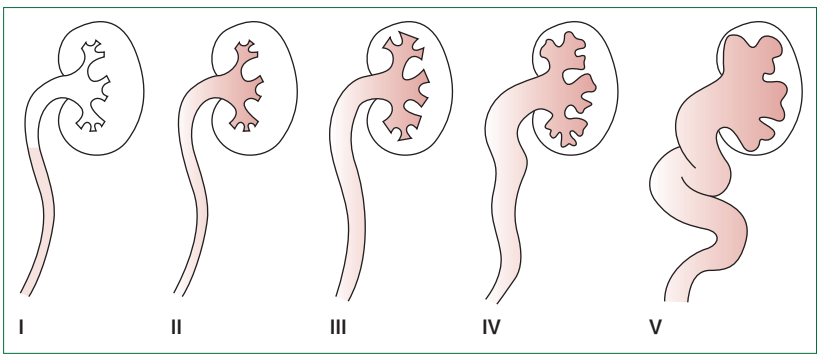

Figure 1: **Grading of vesicoureteric reflux into five grades according to International Reflux Study in Children system**
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Causes

The cause or causes of vesicoureteric reflux are not totally clear. A possibility is that some, particularly low-grade, vesicoureteric reflux is a physiological phenomenon that children grow out of.[14] In children with other urological malformations, high-grade vesicoureteric reflux is frequently a contributory factor. Vesicoureteric reflux can be caused by abnormal positioning of the ureteral orifice, which seems to arise from abnormal ureteric budding, dysfunctional interaction between the ureteric bud and metanephric mesenchyme, or both.[17] Various genes are thought to be involved in bud formation and growth.[14] Many family studies have been done to search for genes causing vesicoureteric reflux in human beings. Feather and coworkers[18] concluded that primary non-syndromic reflux is genetically heterogeneous, with one likely locus at chromosome 1.

Lower urinary tract dysfunction has been suggested to cause vesicoureteric reflux.[19] This relation, however, can work in two directions. High pressure in the bladder can cause vesicoureteric reflux or prevent it from resolving. The presence of vesicoureteric reflux can also affect bladder dynamics and lead to urinary tract dysfunction as the urine in the enlarged ureter or ureters partly refills the bladder after micturition, which hinders total bladder emptying.[20] In the Swedish reflux trial, a significant negative correlation was found between bladder dysfunction and spontaneous improvement of dilating vesicoureteric reflux.[21]

Investigations

Several methods are available to investigate vesicoureteric reflux in children. These include radiological methods, nuclear studies, and ultrasonographic studies.

Micturition urethrocystogram

The gold standard investigation to define vesicoureteric reflux is radiological MCUG. This method is the only one that yields images of the bladder and urethra and enables grading of the reflux according to the International Reflux Study in Children classification. MCUG does, however, have several disadvantages, mostly related to the need for a bladder catheterisation via the urethra, which can be distressing to children[22] and might introduce infection. An additional drawback is the risk of radiation burden. Delay of MCUG until 4–6 weeks after infection was thought to be required to avoid false detection of vesicoureteric reflux, but has been shown not to be needed. Rather, MCUG should be done at the earliest convenient time.[23]

Radionuclide studies

Indirect radionuclide cystography has the advantage that catheterisation is not required and can be done as an add on to an investigation that looks at the renal parenchyma and at the urine drainage from the kidney to the bladder.[24] The most commonly used isotope for indirect MCUG is ^{99m}Tc mercaptoacetyltriglycine (also known as MAG3).[25] The test has 74% sensitivity and 91% specificity compared with a MCUG. Collaboration with the child is essential for this investigation and it should only be used in toilet-trained children. Direct radioisotope cystography can also be done,[26] including in babies and infants, but requires bladder catheterisation and does not provide any anatomical information for the bladder and the urethra.

Ultrasonography

Voiding urosonography is an investigation of the urinary tract with intravesical administration of contrast agent.[27,28] The most widely used instrument is SonoVue (Bracco, Milan, Italy), which uses microbubbles of sulphur hexafluoride. Although children need to undergo catheterisation for this test, there is no radiation and the vesicoureteric reflux can be graded. The contrast agents seem to have very few side-effects.[28] The sensitivity of voiding urosonography is between 57% and 100%, and the specificity is 85–100%.[28] Voiding urosonography seems to grade vesicoureteric reflux higher than MCUG.[29] Nevertheless, this approach is much less frequently used worldwide than MCUG.

Analysis of ureteric doppler waveforms has been suggested as a non-invasive method to detect vesicoureteric reflux.[30,31] The method is based on an analysis of the ureteric jet when the urine comes into the bladder from the ureter. Six patterns have been identified. A monophasic pattern represents an immature form that seems to be more frequent in infants and in children with than without vesicoureteric reflux.[30] The waveform method has been reported to have 88·5% sensitivity and 82·3% specificity compared with voiding urosonography.[32,33] Doppler waveform analysis has not been compared with radiological MCUG, and more work is needed before it can be introduced into clinical practice. A disadvantage of this method is that it cannot grade vesicoureteric reflux.

Several methods are, therefore, available to investigate vesicoureteric reflux. Radiological MCUG is still the most

frequently used, but a non-invasive method would be of great help and might resolve the question on how common vesicoureteric reflux is in the normal population.[34]

Renal scarring

Relation between vesicoureteric reflux and renal scarring

Vesicoureteric reflux, especially of a high grade, is clearly associated with renal parenchymal damage.[35] In many studies intravenous pyelography was mostly used to image the renal parenchyma, although this approach has been overtaken by the use of nuclear imaging, such as dimercaptosuccinyllic acid (DMSA) scintigraphy. These methods, especially DMSA scintigraphy, have greatly improved sensitivity for the detection of uptake defects that might not reflect true loss of renal parenchyma and, therefore, are not possible to visualise with intravenous pyelography.

Two different kinds of uptake defects are related to vesicoureteric reflux: congenital dysplasia and post-infection scars. Which of these kidney lesions is more frequently found is the subject of debate. Some authors claim that much, if not all, of the renal parenchymal damage associated with vesicoureteric reflux leading to end-stage disease is congenital[14] and that vesicoureteric reflux is a poor predictor of renal damage,[36] whereas others emphasise the risks related to postinfection scarring.[2,37] A Swedish study that used intravenous pyelography to define scars concluded that those in boys are mainly congenital dysplasia and those in two-thirds of girls are postinfection scars.[38] Recurrent febrile urinary tract infections, therefore, can cause non-congenital renal scarring, particularly in girls. Thus, the consequences of such postinfection scarring are important to address.

Long-term clinical consequences of postinfection scarring

Several studies have tried to estimate the long-term risk of end-stage renal disease due to previous urinary tract infections. Stark[39] claimed that the risk of a first-time urinary tract infection progressing to end-stage renal failure was one per 10 000 cases. Round and coworkers,[40] however, noted that this estimate was heavily dependent on the assumptions made during calculation, and that numbers as disparate as one per 154 and one per 199 900 cases would be possible to calculate. The major difficulty with calculation of risk is that identification of the cause of end-stage renal failure in adults can be very difficult, and in many registers is imprecise. Craig and colleagues[41] found an association of one case of end-stage renal failure per 10 000 cases of urinary tract infections. A review of the long-term consequences of urinary tract infections emphasised that not enough data exist to define outcomes accurately.[42] Three areas have been highlighted in the literature as important to consider: impaired kidney function, high blood pressure, and complications of pregnancy. Results, however, differ across studies, and prospective, population-based, long-term studies are needed to provide reliable information.

Kidney function

The effects of scarring on kidney function were assessed in all children in Gothenburg, Sweden, who attended a clinic for urinary tract infections in a 10-year period (n=1221).[43] They were followed up for a median of 22 (range 16–26) years after the first infection. At follow-up the median glomerular filtration rate was 99 mL/min per 1·73 m² in children with and without renal scars. Toffolo and coworkers[42] reviewed 19 studies that included more than 3000 children followed up for 0·5–41·0 years. The studies were heterogeneous and many only included patients with severe scarring. The proportion of patients with impaired kidney function at the end of the follow-up, therefore, varied between 0% and 56%. Among the 1029 children from the eight prospective studies assessed, 55 (5·3%) had chronic kidney disease at the end of follow-up.

Blood pressure

Blood pressure was studied in prospective follow-up of the Gothenburg cohort.[44] 24 h blood-pressure monitoring was done in 57 children with renal scarring and results were compared with those from 51 matched children without scars. No difference was found between the groups. Toffolo and colleagues[42] noted, however, that data varied substantially between studies dependent on the children selected; the proportion of children with hypertension ranged from 1·2% to 35·0%.

Complications of pregnancy

Complications of pregnancy owing to kidney scarring were seen in 34 (12%) of 282 pregnancies from five case series.[42] A prospective study monitored 41 women with renal scars during 65 pregnancies. The rates of pre-eclampsia, operative delivery, prematurity, and low birthweight of the children did not differ between women with and without renal scarring.[45] By contrast, a higher rate of pregnancy-related complications was found in a UK study of women with renal scars than in those without.[46]

Data suggest that fewer long-term problems occur in children and adults with postinfection renal scarring than was previously thought. More prospective population-based data with several decades of follow-up are needed.

Natural history of vesicoureteric reflux

Several studies have shown that the vesicoureteric reflux has a high chance of spontaneous resolution. In a population-based prospective study, 230 children with vesicoureteric reflux were followed up for up to 15 years.[47] 168 (73%) of the children with dilating reflux had no or only grade I vesicoureteric reflux at the 10-year follow-up

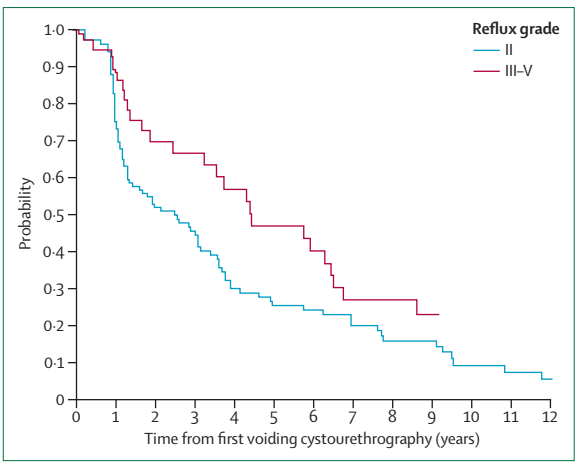

***Figure 2*: Probability of disappearance of vesicoureteric reflux over time**
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(figure 2). Non-dilating reflux disappeared more quickly than dilating reflux. In another study, 735 children with vesicoureteric reflux were followed up for a mean of 76 months.[48] For grade I–II reflux the median time to resolution was 38 months, for grade III 98 months, and for grade IV–V 156 months.

Timing of imaging

MCUG used to be included as an investigation in all guidelines for the assessment of children with urinary tract infections.[49] In UK and the USA, however, this approach is suggested for only a select group of children.[3,4] The American Academy of Pediatrics guidelines state that MCUG should not be performed routinely after the first febrile urinary tract infection in children aged 2 months to 2 years unless ultrasonography reveals hydronephrosis, scarring or other findings suggestive of high-grade vesicoureteric reflux or obstructive uropathy or other atypical or complex clinical disorders.[3] The UK National Institute for Health and Care Excellence also supports limited use of MCUG and provides a detailed list of circumstances under which it may be considered (panel).[4] These risk factors include infection with bacteria other than *Escherichia coli*. Most infectious *E coli* strains have P fimbriae that can attach to the uroepithelial cell lining,[50] whereas other bacteria rely on host factors to be able to cause an infection and, therefore, the chances of a urinary tract abnormality are much higher in children with non-*E coli* infections.

The guidelines from the European Association of Urology recommend an active approach, including the use of MCUG in all children younger than 2 years once a first febrile urinary tract infection is confirmed.[20] An alternative approach is the so-called top-down approach. Many children with dilating vesicoureteric reflux have positive findings on DMSA scintigraphy.[51] The guidelines, therefore, suggest that MCUG could be limited to children with early positive DMSA scintigraphy findings.

***Panel*: Modified UK National Institute for Health and Care Excellence guidelines on risk factors for structural abnormalities that require imaging after a first febrile urinary tract infection[4]**

- Serious illness
- Poor urine flow
- Abdominal or bladder mass
- Raised creatinine concentration in serum
- Septicaemia
- Failure to respond to treatment with suitable antibiotics within 48 h
- Infection with an organism other than *Escherichia coli*
- Procalcitonin concentration >0·5 ng/mL
- Recurrent infections

In a meta-analyses of 13 cohort studies, Mantadakis and colleagues[52] showed that DMSA scintigraphy had 79% sensitivity and 53% specificity in eight studies with findings from individual patients, and 60% and 65%, respectively, in five studies with findings at the renal unit level. They concluded that acute-phase DMSA scintigraphy cannot be recommended as replacement for MCUG in the assessment of young children with a first febrile urinary tract infection.

Ultrasonography has in some studies been surprisingly helpful to predict vesicoureteric reflux. Sensitivities of 86%, 66% and 83% have been reported in three studies that involved more than 1400 children.[53–55] Other studies have investigated the possibility of using inflammatory markers in serum during infection to identify children who might develop high-grade reflux. A meta-analyses of 12 studies involving 526 patients showed that procalcitonin concentrations higher than 0·5 ng/mL had 83% sensitivity and 43% specificity for grade III or higher vesicoureteric reflux.[56]

An Italian study involving 304 children compared the yield, cost, and radiation burden of investigations recommended in five different guidelines.[57] The top-down approach showed the highest sensitivity (76%), compared, for example, with the National Institute for Health and Care Excellence (29%) and American Academy of Pediatrics guidelines (27%). This advantage, however, was associated with substantially higher economic cost and radiation burden. The authors concluded that no ideal diagnostic protocol existed, and that while aggressive protocols had higher sensitivity, the increased financial and radiation costs made the benefits questionable.[57]

Treatment

The main aims when treating vesicoureteric reflux are to reduce the number of recurrent febrile urinary tract infections and the risk of further renal scarring. Treatment of the vesicoureteric reflux itself is not recommended, as sterile vesicoureteric reflux is not deemed to be a risk factor for renal scarring.[20] Treatment

decisions need to be made on an individual basis, taking into account age, reflux grade, history of previous febrile urinary tract infections, existing kidney scarring, other urogenital malformations, adherence to medical treatment, and the patient's preferences.

Conservative first-line therapy is favoured both by most paediatric nephrologists and urologists in most clinical situations.[4,20] Treatment focuses on bladder function but might include prophylactic use of antibiotics aimed at reducing the number of recurrent urinary tract infections. Parents should be encouraged to have urine tested early if the child has a febrile infection without a clear focus and to ensure that their child receives early treatment if the urine test suggests a urinary tract infection even before urine culture results are available.[4]

Prophylactic antibiotics

Prophylactic antibiotics have been used for several decades to prevent urinary tract infections in children with and without vesicoureteric reflux, although the scientific background for this approach is weak. The UK National Institute for Health and Care Excellence concluded in their 2007 guidelines that the prophylactic use of antimicrobials was not scientifically supported.[4] Several studies of prophylactic antibiotics have been reported since then. They have, however, all been small, included children without vesicoureteric reflux or with only low-grade reflux, or did not use placebo or masking of treatment.

Garin and coworkers[58] studied 236 children who had had an episode of acute pyelonephritis between age 3 months and 18 years, of whom 218 completed follow-up. Among these 218 children, vesicoureteric reflux was found in only 113 (52%), with grade III reflux being the most severe and seen in only 37 children. The children were randomised to receive either prophylactic antibiotics or no treatment. No difference was found between treatment groups in the rates of development of new renal scarring. In a study by Roussey-Kesler and colleagues,[59] 225 children aged 1 month to 3 years were randomised to receive either prophylaxis with co-trimoxazole or no treatment. After 18 months of follow-up the numbers of recurrent urinary tract infections (all or febrile) were similar in the two groups. Two Italian studies that included a total of 438 children also found no difference in recurrence of febrile urinary tract infections and development of new renal scars between children who did and did not receive prophylactic antibiotics.[60,61] Montini and colleagues[60] included children without vesicoureteric reflux or with vesicoureteric reflux up to grade II in their study,[60] and Pennesi and coworkers[61] studied 100 children with grade II–IV vesicoureteric reflux between ages 1 month and 3 years.[61]

A large Australian study of 576 children randomised to either prophylactic co-trimoxazole or placebo for 12 months was reported by Craig and coworkers.[62] Children were enrolled over nearly 10 years and the study was terminated early owing to slow recruitment. Those with any grade of vesicoureteric reflux or no reflux were eligible. The primary endpoint was recurrence of any urinary tract infection. Children who received co-trimoxazole had a recurrence rate of 13% compared with 19% of those given placebo (p=0·02), the difference was maintained in subgroup analyses. The findings showed that 14 children would need to be treated for 1 year to prevent one urinary tract infection.

In the Swedish reflux trial[21,63–66] 203 children aged between 1 and 2 years who had grade III or IV vesicoureteric reflux were randomised to one of three groups: low-dose prophylactic antibiotics (n=69); endoscopic treatment with dextranomer and hyaluronic acid (n=66); or surveillance with early antibiotic treatment if a urinary tract infection occurred (n=68). No reflux was detected 2 years after randomisation in 13%, 38%, and 15% of children, respectively.[66] The results were initially better in the group that received dextranomer and hyaluronic acid, but 20% of those children had recurrent dilating vesicoureteric reflux after 2 years. Recurrent febrile urinary tract infections occurred in 42 (33%) of 128 girls and in seven (9%) of 75 boys studied.[63] The proportions of recurrent infections differed significantly between the treatment and surveillance groups: 19% of girls receiving co-trimoxazole prophylaxis and 23% of those receiving dextranomer and hyaluronic acid versus 57% of those surveyed (p=0·0002). New renal scarring developed in 13 (10%) girls and two (3%) boys.[65] New renal scars developed in 6% of children treated with co-trimoxazole, 12% treated with dextranomer and hyaluronic acid, and 18% undergoing surveillance. The difference was significant for prophylaxis versus surveillance (p<0·0005) but not for other comparisons.

The American Academy of Pediatrics did a meta-analysis of 1091 infants aged 2–24 months included in six studies (figure 3). They found no differences between children who had been given prophylactic antibiotics and those who had received no treatment or placebo. This finding was independent of the occurrence of reflux and grade of vesicoureteric reflux. The data, however, were related only to the degree of vesicoureteric reflux but not to sex.[3]

The RIVUR study, which was done in the USA, invovled 607 children (558 girls and 49 boys) with grade I–IV vesicoureteric reflux 19 paediatric centres, although most (80%) had grade II or III reflux.[67] Participants were treated with prophylactic antibiotics or placebo for 2 years. Reccurent urinary tract infections developed in 39 (13%) of 302 children who recevied prophylaxis compared with in 72 (24%) of 305 who received placebo (relative risk 0·55, 95% CI 0·38–0·78). The rates of development of renal scarring, however, did not differ between groups (12% *vs* 10%).[68] In a double-blind study in India, 93 children with grade I–IV vesicoureteric reflux were randomised to receive either co-trimoxazole or placebo for 12 months. Of note was the finding that

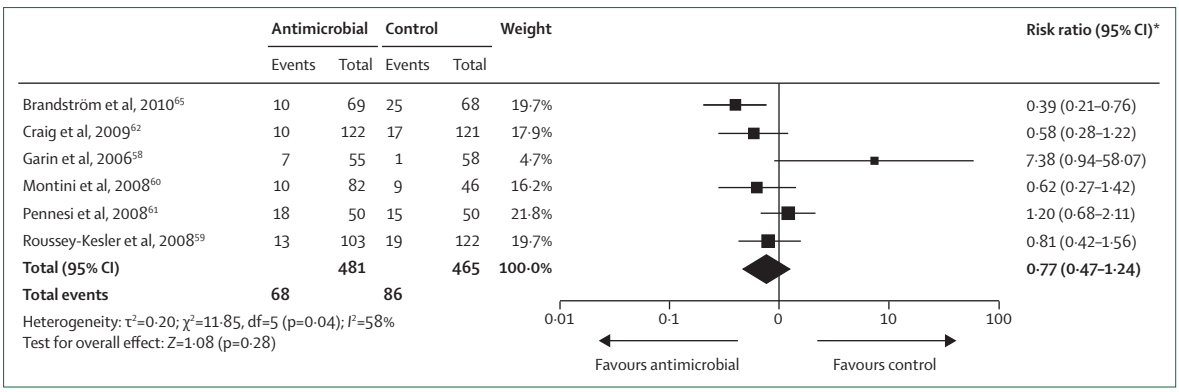

Figure 3: **Meta-analyses of the relation between the use of prophylactic antibiotics and renal scarring in children aged 2–24 months with any grade of vesicoureteric reflux**

No difference was found between children treated with antibiotics and controls. *Calculated with Mantel-Haenszel random effects model. Reproduced from reference 3 by permission of the American Academy of Pediatrics.

the children receiving prophylaxis developed significantly more recurrent infections than those receiving placebo (21% *vs* 6%, p=0·02; Hari P, All India Institute of Medical Sciences, personal communication).

Antimicrobial prophylaxis increases the risk that a later infecting bacterial strain will be resistant to antibiotics and, therefore, the issue of whether long-term antibacterial prophylaxis is beneficial is important to resolve. Children who have received long-term prophylaxis have recurrent urinary tract infections with strains of *E coli* more resistant to ampicillin, compound preparations of amoxicillin and clavulanic acid, and co-trimoxazole than children who have not been given prophylactic treatment.[69] A meta-analysis showed that this risk was reduced for children who had received nitrofurantoin compared with those who had received co-trimoxazole.[70]

Bladder treatment

Bladder dysfunction is a recognised risk factor for the persistence of vesicoureteric reflux. In the prospective Swedish reflux trial, 41 (20%) of the 203 infants assessed had lower urinary tract dysfunction at study entry, which had increased to 69 (34%) 2 years later.[21] Bladder dysfunction at baseline, however, did not predict the outcome of the study at 2 years. No prospective randomised study has looked at the outcome of vesicoureteric reflux and recurrent infections after the treatment of the bladder dysfunction.

Surgical treatment

Correction of vesicoureteric reflux has been done surgically for many years. The main approaches are ureteric reimplantation or the injection of a bulking agent below the ureteric orifice.[71]

Ureteric reimplantation

Ureteric reimplantation can be done through several different techniques, although they all share the basic principle of lengthening the intramural part of the ureter. All techniques have excellent results with few complications and success rates of 92–98%.[72] The most widely used technique is Cohen's cross-trigonal reimplantation.[20]

Surgical correction of vesicoureteric reflux has been compared with conservative antibiotic prophylaxis in three studies. The Birmingham reflux study randomly allocated 96 children to operative or non-operative treatment and followed them up for 5 years.[73] No differences were found between the two groups for breakthrough urinary tract infections, kidney function, or the formation of new scars. The European branch of the International Reflux Study in Children studied 306 children with grade III–IV vesicoureteric reflux.[74] Of these, 155 children were given medical treatment and 151 underwent surgical treatment. Scarring was monitored with intravenous urography. After 5 years, 19 (13%) children in the medical and 20 (13%) in the surgical group had developed a new scar. All children were followed up for 10 years and only two further renal scars developed.[75,76]

Smellie and coworkers[77] randomly assigned 52 children with grade III–IV vesicoureteric reflux to surgical or medical treatment and assessed glomerular filtration rate, measured by plasma clearance of ^{51}Cr-edetic acid, for 10 years. No differences were found in the change of glomerular filtration rate between the two groups. Four children, two in each group, developed end-stage renal failure.

A meta-analysis reviewed data from eight trials involving 859 children. Surgical correction of vesicoureteric reflux together with antibiotic prophylaxis was associated with a 60% reduction in recurrent febrile urinary tract infections at 5 years, but no concomitant significant reduction was seen in progressive renal damage (relative risk 1·05, 95% CI 0·85–1·29).[78]

Laparoscopic and intravesical surgical approaches have been developed. They have longer operative times than traditional surgical approaches, and the European Association of Urology guidelines do not recommend

them for routine use, although they can be offered as alternative approaches in experienced centres.[20]

Injection of bulking agents

Injection of a bulking agent below the ureteric orifice was developed in the 1980s.[79] The original agent was Teflon, which had a good success rate for reducing the grade of vesicoureteric reflux. Teflon, however, can migrate to the lungs and the brain and, therefore, has been largely abandoned.[80,81] Further agents have been developed, and the most commonly used is combined dextranomer and hyaluronic acid.[82] The results with this agent on resolution of vesicoureteric reflux are not as good as those from open surgery, but it is much less invasive. A meta-analysis including 5527 patients showed resolution rates of 79% for grade I and II vesicoureteric reflux, 72% for grade III, 63% for grade IV, and 51% for grade V after endoscopic application of dextranomer and hyaluronic acid.[83] Another review of 47 studies reported similar findings.[84] The results can be improved by repeating the procedure, as is common practice, but vesicoureteric reflux frequently recurs with time.

The Swedish reflux trial has compared the use of dextranomer and hyaluronic acid with that of antimicrobial prophylaxis, surveillance, or both.[63,65] No significant differences could be found between the dextranomer and hyaluronic acid group and either the antimicrobial prophylaxis or surveillance groups for recurrent febrile urinary tract infections or further renal scarring after 2 years. Prophylaxis and surveillance differed significantly in favour of prophylaxis.

Circumcision of healthy infant boys has been associated with significantly reduced numbers of cases of acute pyelonephritis, which can lead to renal scarring.[85] A meta-analysis of more than 400 000 boys showed that the odds ratio for circumcised boys was 0·13 (95% CI 0·08–0·20).[86] The data are much weaker in children with urological malformations, such as high-grade vesicoureteric reflux, but do still suggest a benefit.[87,88]

Sibling screening

Screening of siblings of children with known vesicoureteric reflux has been advocated, and has revealed a prevalence of 27·4%.[15] The UK National Institute for Health and Care Excellence and the American Academy of Pediatrics guidelines do not discuss screening, but since they recommend use of MCUG only in selected children after a urinary tract infection, it is reasonable to suppose it is not endorsed. The European Urology guidelines give no recommendation other than screening should be avoided in children who are already toilet trained, whereas the decision for younger siblings is left to individual urologists.[20] The American Urological Association recommends screening of siblings who have evidence of renal cortical abnormalities, renal size asymmetry, or a sibling with a urinary tract infection.[15]

Conclusions

The management of vesicoureteric reflux in children is a controversial area, but advances have been made towards less aggressive management than that applied traditionally. Most guidelines recommend that radiological MCUG is not used routinely and is limited to highly selected cases, although it remains the gold standard to define vesicoureteric reflux, at least in babies and infants. Whether to use antibiotic prophylaxis also remains controversial. Most guidelines do not recommend routine prophylaxis, but this approach does have a role in children, mainly girls, with high-grade vesicoureteric reflux and recurrent febrile urinary tract infections. Open surgery has largely been replaced by the injection of a bulking agent close to the ureteric orifice in the bladder. Although studies have shown no benefits of surgery over prophylactic antibiotics, the injection method has only been compared with prophylaxis in one trial. Antibiotic prophylaxis yielded better results, but further investigation is warranted.

Declaration of interests

I declare no competing interests.

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