Endoscopic treatment of vesicoureteral reflux: current practice and the need for multifactorial assessment

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Abstract: Vesicoureteral reflux (VUR) affects around 1% of all children. It carries an increased risk of febrile urinary-tract infections (UTIs) and is associated with impaired renal function. Antibiotic prophylaxis is an established approach to managing the condition, but it does not protect against UTI and encourages bacterial resistance. Ureteral re-implantation (open surgery) is a relatively traumatic procedure typically requiring hospitalization, and there is a risk of significant post-treatment complications. Endoscopic treatment with NASHA/Dx gel (Deflux®) is minimally invasive, well tolerated and provides cure rates approaching those of open surgery: 80–90% in several studies. It has also been shown to be effective in a variety of ‘complicated’ cases. Thus, endoscopic treatment is generally preferable to open surgery and long-term antibiotic prophylaxis. Non-treatment of VUR is being discussed as an alternative option, although this mainly appears suitable for children with low-grade reflux and normal kidneys. A new approach to managing VUR may be considered, with treatment decisions based not only on the grade of reflux but also on factors such as age, sex, renal scarring and bladder dysfunction. Open surgery would be reserved only for use in the 10–15% of children not responding to endoscopic treatment and those with severe ureteral anomalies.

Keywords: Vesicoureteral reflux, deflux, NASHA/Dx gel, antibiotic prophylaxis, ureteral re-implantation

Introduction

Vesicoureteral reflux (VUR) affects around 1% of all children, making it the most common paediatric anomaly of the urinary tract [Jacobson *et al.* 1999]. Febrile urinary-tract infection (UTI) during infancy or childhood is a recognized marker for abnormalities of the urinary tract, the most common being primary VUR (around a third of children with UTIs have VUR [Hodson *et al.* 2007]). UTIs in children with VUR are more likely to reach the upper urinary tract and develop into pyelonephritis than in children without VUR [Kirsch *et al.* 2006]. In turn, pyelonephritis is associated with febrile illness and a possible risk of renal scarring; permanent renal damage has also been reported in a large number of children with recurrent UTIs [Orellana *et al.* 2004].

VUR tends to resolve spontaneously over time, particularly in children with low-grade reflux and normal kidneys. However, in many patients it can persist for a number of years, in some cases

into adulthood [Smellie *et al.* 2001]. The likelihood of VUR persisting depends on several factors including reflux grade – in one study of 179 girls and 35 boys (mean age 4.2 years), reflux grades I–III resolved at an annual rate of 13% for the first 5 years, compared with 5% for grade IV reflux [Schwab *et al.* 2002]. Figure 1 shows resolution rates from this study for high- versus low-grade reflux. The authors also found that bilateral reflux resolves more slowly in cases of bilateral versus unilateral reflux, and more rapidly in girls versus boys. In the International Reflux study, lower resolution rates were observed among 149 children with grade III–IV reflux (5-year resolution rate of 15%) [Smellie *et al.* 2001]. The impact of age on VUR resolution was also reported in a study of 115 infants with grade III–V reflux: resolution of grade IV–V reflux was high during the first year of life, particularly among boys (29%) [Sjöström *et al.* 2004]. Notably, many recent studies of VUR resolution have focused on infants and young children up to the age of 2 years. This was the case, for example,

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Figure 1. Spontaneous resolution of vesicoureteral reflux: low grades [I–III] versus high grades [IV–V] [Schwab CW Jr, *et al.* 2002]. Between-group difference, $p=0.012$. Reproduced with permission.

in two Swedish studies of spontaneous resolution of VUR [Wahll *et al.* 2009; Sillén *et al.* 2007].

The fact that reflux may persist for a number of years provides the rationale for treating VUR. It has been shown that adults with persistent reflux and scarring may run the risk of further pyelonephritis, progressive renal disease and hypertension [Martinell *et al.* 1996, 1995], and VUR is likely a major factor in the pathogenesis of recurrent UTI, acute pyelonephritis and renal scarring [Faust *et al.* 2009]. Thus, the aims of treatment are to reduce the risk of febrile UTIs affecting the upper urinary tract and, possibly, protect against future renal damage.

Treatments for VUR may be classified into three main different types: antibiotic prophylaxis, open surgery and endoscopic treatment. The primary aim of this article is to summarize our current knowledge and experience of endoscopic treatment of VUR, and discuss the role of this therapy relative to other treatment options. In addition, the classification of VUR will be examined, as it is becoming apparent that treatment decisions should be based not just on the grade of reflux, but also aspects such as bladder function and renal status. Accordingly, we will first examine the relationship between VUR and bladder dysfunction.

VUR and bladder dysfunction

It has been reported that approximately 20% of children with VUR also have dysfunctional

voiding, the risk being independent of sex, laterality or severity of reflux [Homayoon *et al.* 2005]. Reflux during bladder filling without increased pressure ('passive' reflux) is associated with high bladder capacity, and this has a lower resolution rate than reflux occurring during micturition [Wahll *et al.* 2009]. Other authors have also reported an association between bladder dysfunction and the reduced likelihood of VUR resolution [Yeung *et al.* 2006; Sjöström *et al.* 2004].

Bladder dysfunction has typically been regarded as a cause of VUR. Thus, children with both conditions first undergo urotherapy, on the basis that cure of bladder dysfunction will also cure VUR. However, in some cases both conditions persist despite urotherapy, and endoscopic treatment of such children is viable. A study published in 2007 showed that NASHA/Dx gel (Deflux®) treatment provided an 83% resolution rate among children with VUR and bladder dysfunction [Läckgren *et al.* 2007], similar to expectations of efficacy in children with VUR alone. In 59% of the patients, bladder dysfunction was also resolved following endoscopic treatment. New data from other authors also show improved bladder dysfunction following NASHA/Dx gel therapy for VUR, despite the failure of previous urotherapy [Williams *et al.* 2009]. Furthermore, a study of urotherapy among children with high bladder capacity and high-grade VUR showed that the urotherapy had no impact on the rate of spontaneous resolution [Sillén *et al.* 2007]. Taken together, these data indicate that VUR

may, in some cases, cause bladder dysfunction. However, the precise relationship between the two conditions remains to be defined.

Options for managing VUR

Antibiotic prophylaxis

The rationale for antibiotic prophylaxis is the prevention of UTI, thereby minimizing the risk of pyelonephritis and renal damage. Therapy is often continued until VUR resolves spontaneously, which often takes a number of years. Owing to this dependence on spontaneous resolution, antibiotic prophylaxis is considered most suitable for patients with low-grade VUR. The most commonly used antibiotics in the treatment of VUR are trimethoprim-sulfamethoxazole (TMP-SMX), trimethoprim alone and nitrofurantoin [Bollgren, 1999].

Patients and their parents often view antibiotic prophylaxis positively because the other treatment options for VUR involve invasive procedures. However, increasing antibiotic resistance rates are a major problem with this approach to treating VUR. TMP-SMX resistance in excess of 30% has been reported [Jones *et al.* 2004], and a 23-fold increase in the risk of TMP-SMX resistance has been reported among children receiving antibiotic prophylaxis [Allen *et al.* 1999]. Long-term antibiotic prophylaxis is likely to increase the risk of resistance because inadequate dosing (inevitable during long-term therapy) exposes bacteria to reduced levels of the drug, encouraging selection of resistant strains. A study of urine samples from children taking antibiotic prophylaxis for VUR showed sub-therapeutic concentrations of TMP-SMX in almost one-third of the samples [Pomeranz *et al.* 2000]. There are few treatment options for infections involving bacteria resistant to multiple antibiotics, and the spread of resistant strains can affect the community as a whole. As well as contributing to the development of bacterial resistance, inadequate adherence to the dosing regimen will leave the patient vulnerable to breakthrough infections [Bollgren, 1999]. Even in the clinical-trial setting, where compliance is likely to be higher than in routine practice, breakthrough infections are reported in 30–40% of VUR patients over a 5-year period of antibiotic prophylaxis [Arant, 1992; Jodal *et al.* 1992]. In a systematic review published in 2006, five studies comparing long-term antibiotic therapy with placebo or no treatment showed a relative risk of repeat positive urine culture of 0.44

(95% confidence interval: 0.19–1.00) [Williams *et al.* 2006]. The authors concluded that large, properly randomized, double-blinded studies are needed to improve the evidence base, and more recent studies have indicated that antibiotic prophylaxis is not effective. In a 12-month study of 338 children who had experienced a first febrile UTI, children receiving antibiotic prophylaxis were no less likely to experience recurrent febrile UTI than those not receiving prophylaxis [Montini *et al.* 2008]. A second study with 4 years' follow-up showed a lack of difference in the incidence of pyelonephritis and renal damage among children with VUR who received antibiotic prophylaxis, and those who did not [Pennesi *et al.* 2008]. Another study comparing antibiotic prophylaxis with no treatment among children with VUR (grades I–III) also showed no overall difference in the incidence of UTI, although there was a significant reduction among boys receiving prophylaxis, particularly those with grade III reflux [Roussey-Kesler *et al.* 2008]. The lack of effect of antibiotic prophylaxis, with respect to UTI incidence, has similarly been shown in children with and without VUR [Conway *et al.* 2007; Garin *et al.* 2006] (i.e. diagnosed with UTI or pyelonephritis). Taking all the above factors into account, long-term antibiotic prophylaxis cannot be considered as a viable option for managing children with VUR.

Anti-reflux surgery – ureteral re-implantation

Open surgery involves re-implanting the ureter(s) to increase its intramural length at the ureterovesical junction. This has been the 'gold standard' for the treatment of high-grade VUR over the last 50 years. The cure rate, dependent on the procedure and the severity of reflux, is generally high. For a single surgical procedure, the cure rate is 95–99% for reflux grades I–IV, while for grade V reflux it is approximately 80% [Lavine *et al.* 2001; Elder, 2000; Duckett *et al.* 1992]. In comparison with other treatment options for VUR, however, open surgery is a major invasive procedure that is traumatic for patients. A hospital stay is typically required and post-operative pain is common, although improvements in surgical techniques (extravesical and/or laparoscopic) and post-operative pain relief have, in recent years, shortened hospital stays and reduced the extent of post-operative discomfort. Intravesical laparoscopy for ureteral re-implantation has been investigated [Thakre and Yeung, 2008; Callewaert, 2007; Heidenreich *et al.* 2004] and, although this offers the potential for reducing

post-operative discomfort and recovery time, it has not yet become widely used. Complications can occur following open surgery and ureteral obstruction is a major potential problem, affecting approximately 2% of patients who usually require re-operation [Elder *et al.* 1997]. Other complications may include post-operative bleeding and bladder dysfunction. The overall complication rate following surgery varies according to the surgical technique, and has been reported as 2% with the Cohen Cross-Trigonal technique (intravesical) and 1–7% with the extravesical method [Ellsworth *et al.* 2000]. In addition, the costs of open surgery are relatively high, mainly due to the requirement for hospitalization.

Non-treatment (short-term antibiotics)

Recently, the possibility of not actively treating VUR has been proposed, whereby antibiotic therapy is administered only when UTIs occur [Faust and Pohl, 2007]. This approach could be considered as an alternative to long-term prophylaxis. Arguments in favour of this approach include the high spontaneous cure rate of VUR, lack of reduction in renal complications associated with treatment, and the possibility that VUR may be caused by bladder dysfunction (treat the bladder instead) [Faust and Pohl, 2007; Hodson *et al.* 2007]. In addition, the risks of bacterial resistance are lower than with long-term prophylaxis. On the other hand, there are several strong arguments against non-treatment. Strict control of patients is required and treatment is required without delay upon emergence of an infection. This can cause practical difficulties, particularly in developing countries where access to antibiotics is often limited. Cure of VUR is associated with a reduction in febrile UTI/pyelonephritis, [Hodson *et al.* 2007] thereby decreasing overall morbidity. VUR persists for at least 5–10 years in many cases [Smellie *et al.* 2001] (particularly high-grade reflux associated with scarred kidneys [Godley *et al.* 2001]), placing susceptible kidneys at potential risk of progressive renal damage. Also, despite the widely held belief that bladder dysfunction causes VUR, there is now evidence that VUR may cause bladder dysfunction (it is of course possible that both of these scenarios may be true to some extent, with variation between cases) [Williams *et al.* 2009; Läckgren *et al.* 2007]. Patients with VUR causing bladder dysfunction, and those with persistent VUR with bladder dysfunction and recurrent UTI, are difficult to treat conservatively and early cure of VUR is clearly beneficial.

Therefore an active treatment is indicated. Children with VUR who are treated successfully have no need for further monitoring, in contrast to children with continuing VUR who likely require an increased number of late voiding cystourethrogram (VCUG) investigations, which are traumatic for children and carry a risk of morbidity [Kirsch *et al.* 2006]. Finally, there is a possibility that high-grade VUR in infants may delay maturation of bladder function.

Endoscopic injection

Endoscopic treatment involves submucosal injection of a bulking agent into the bladder wall below the ureteral orifice, or within the ureteral tunnel, to provide tissue augmentation. It is a minimally invasive procedure, offering a high chance of cure through a single intervention. The choice of injectable agent is key to the success of endoscopic treatment. To ensure safety and long-term efficacy, the ideal injectable agent should be biocompatible. The risk of new renal scarring is greatest among infants and young children aged under 5 years [Olbing *et al.* 2003]. Therefore, the bolus created using an injectable agent should persist for a minimum of 5 years. NASHA/Dx gel – dextranomer microspheres in a stabilized hyaluronic acid-based gel of non-animal origin – was developed specifically for endoscopic treatment. Pre-clinical studies demonstrated the biocompatibility of NASHA/Dx gel, together with a lack of potential for migration from the injection site [Stenberg *et al.* 1999; Stenberg *et al.* 1997]. Both constituents of NASHA/Dx gel are biodegradable polysaccharides, ensuring that this material cannot accumulate permanently within the body. Injected NASHA/Dx gel becomes infiltrated with endogenous connective tissue, and follow-up studies (both preclinical and clinical) have shown that the bolus persists for at least 3 years with no fibrosis or aggressive granulomatous reaction spreading to adjacent tissue [Läckgren *et al.* 1999; Stenberg *et al.* 2003]. Long-term clinical data indicate that NASHA/Dx gel remains effective for much longer than this, over a period of 7–12 years, and only 3% of patients experienced a febrile UTI over that period [Stenberg and Läckgren, 2007]. Currently, NASHA/Dx gel is the dominant injectable agent for endoscopic treatment of VUR and, accordingly, it will be the only injectable agent discussed for the remainder of this article.

Efficacy (VUR resolution)

The first major study of endoscopic treatment with NASHA/Dx gel involved 228 children with VUR; ureters with reflux grade II–V were treated with up to three NASHA/Dx gel injection procedures. The study included long-term clinical follow-up (mean duration 5 years), and a VCUG was performed in 49 children (median 3 years after the last endoscopic treatment). At their last VCUG, 68% of patients had reflux grade 0 or I and were therefore considered to be cured [Stenberg and Läckgren, 2007; Läckgren *et al.* 2001].

More recent studies have reported much higher overall success rates with endoscopic treatment, approaching those seen with open surgery (in the region of 90%), after up to 12 months' follow-up [Yu and Roth, 2006; Kirsch *et al.* 2004; Puri *et al.* 2003]. The VUR cure rate has also been shown in a randomized, prospective study to be significantly higher following NASHA/Dx gel than with 12 months of antibiotic prophylaxis [Capozza and Caione, 2002]. However, there is an apparent learning curve with the treatment procedure: in one study, success rates increased from 60% for the first 20 of 134 patients treated, to 80% for the last 20 cases [Kirsch *et al.* 2003]. Many patients respond to a single treatment: in two studies, around three-quarters of patients were cured (reflux grade 0) at 3 months [Wadie *et al.* 2007; Kirsch *et al.* 2003] and, in another study, reflux was corrected in 86% of ureters at 3–12 months' follow-up [Puri *et al.* 2003]. Nevertheless, in patients not responding to the first procedure, repeat endoscopic injection is viable [Läckgren *et al.* 2001].

Many investigators have observed a lack of reflux in VCUG assessment performed immediately after endoscopic injection, but 'recurrent' VUR may appear at 3 or 12 months. Consequently, there is a risk of recurrent VUR after the first endoscopic treatment [Lee *et al.* 2009], and the long-term success rate after one injection can be expected to be 60–80% depending on primary grade of reflux, injection technique and other factors. In one study, of ureters free from reflux at 12 months, only 4% developed recurrent dilating reflux. This was generally related to persistent bladder dysfunction and/or UTI (i.e. the patients were symptomatic) [Läckgren *et al.* 2001]. These data, and longer-term clinical studies reporting very low risk of UTI after treatment [Läckgren *et al.* 2007], indicate that the rate of

recurrence is low after the first year. These data are consistent with the histopathological data indicating long-term persistence of the bolus created by NASHA/Dx gel endoscopic treatment [Stenberg *et al.* 2003].

Cure rates may be optimized by using the hydrodistention-implantation technique (HIT), a modified version of the original subureteral transurethral injection (STING) technique. The more recent technique involves injection of NASHA/Dx gel into the mucosa of the ureteral tunnel, while a pressured stream of irrigation fluid is directed into the ureter to keep it open. VUR cure rates have been reported to be significantly greater among children treated via the HIT (89%), compared with the standard STING method (71%) [Kirsch *et al.* 2004]. However, it should be acknowledged that adoption of HIT is not guaranteed to improve cure rates, as shown in a recent study comparing HIT with intra-orifice injection of NASHA/Dx gel where there was no significant difference between the two approaches [Gupta and Snodgrass, 2008].

Most reports on spontaneous resolution of VUR involve patients below 2 years of age, with annual resolution rates around 15%. However, most studies of endoscopic treatment involve children with a mean age > 4 years, and dilating reflux in these patients is unlikely to resolve. This has been shown in the International Reflux Study, which reported a very high risk of reflux persisting for 5 or even 10 years in children aged 4–11 years [Smellie *et al.* 2001]. It is therefore important to consider the efficacy of endoscopic injection in the context of the patients' age. The NASHA/Dx gel data reported by our own group included children with a mean age of 4–5 years [Stenberg and Läckgren, 2007; Läckgren *et al.* 2001]. Reflux would be far more likely to persist in this age-group (compared with the younger children in spontaneous resolution studies), strengthening the indication for active treatment.

Several studies have shown that endoscopic treatment is effective in VUR patients with complicating factors. The cure rate following NASHA/Dx gel treatment in children with VUR and duplicated ureters was 63%, while for those with a small kidney (1 kidney contributing 10–35% of total renal function) the cure rate was 70% [Läckgren *et al.* 2003]. More recently, successful experience in children with VUR and bladder dysfunction was documented. [Läckgren

et al. 2007] Another study included children with a variety of different complications, including failure to respond to open surgery, duplicated ureters, neurogenic bladder and ectopic ureters [Perez-Brayfield *et al.* 2004]. While the numbers of patients in some of these sub-groups were small, success rates were high, indicating that endoscopic treatment should be considered as an option in children with a wide range of complications.

Safety and tolerability

A number of studies have shown that almost all children treated endoscopically did not experience any significant complications or adverse events. This was observed in the first clinical study of NASHA/Dx gel for VUR [Stenberg and Läckgren, 1995], and also in the first large-scale study (310 procedures in 228 children with VUR) [Läckgren *et al.* 2001]. There was a similar lack of complications in a subsequent study involving 113 children [Puri *et al.* 2003]. In another study, the only adverse event was mild, transient flank pain, affecting 2/120 patients [Yu and Roth, 2006]; flank pain or emesis affected 4% of children in a further study [Kirsch *et al.* 2004]. There have been isolated cases of ureteral obstruction or hydronephrosis following endoscopic treatment with NASHA/Dx gel [Snodgrass, 2004], but the overall incidence of this has been estimated to be less than 0.7% [Vandersteen *et al.* 2006]. Ureteral obstruction may be treated using a stent, with resolution likely within 7–30 days. A further possible complication following endoscopic treatment is *de novo* reflux in the contralateral (untreated) ureter, among children treated for unilateral reflux. This is a recognized complication of both surgical procedures and endoscopic injection. In one study, contralateral reflux was reported to affect 6/134 patients (4.5%) [Kirsch *et al.* 2003]. A more recent study showed the incidence of contralateral reflux to be 10.1%, and the grade of reflux was I–II in 49% of these patients [Menezes *et al.* 2007]. The authors concluded that prophylactic treatment of non-refluxing contralateral ureters (during the treatment procedure for unilateral reflux) is not warranted, due to the low grade and low incidence of *de novo* reflux.

Histological findings confirm the lack of adverse reactions to NASHA/Dx gel. In a study published in 2003, 13 patients who responded poorly to endoscopic treatment underwent open surgery

to cure their reflux [Stenberg *et al.* 2003]. The implanted NASHA/Dx gel and surrounding tissue were resected, and histological analysis showed a mild, granulomatous reaction of the giant-cell type, as expected for the implantation of any foreign material. In another histopathological study, a similar giant-cell reaction to NASHA/Dx gel was observed and, although there was evidence of increased inflammatory reaction over time (3–22 months), there were no increases in nuclear turnover or fibrosis [Routh *et al.* 2007]. A study of NASHA/Dx gel in rats indicated granuloma formation in 43% of cases, along with giant-cell and inflammatory reactions [Alkan *et al.* 2007]; no clinically significant granuloma formation has been reported with NASHA/Dx gel injection in humans. Overall, both the clinical and histological data for NASHA/Dx gel are consistent with the biocompatible nature of this material and the initial, favourable preclinical data [Stenberg *et al.* 1999].

Post-treatment incidence of urinary tract infections

Low rates of febrile UTI have been observed following endoscopic treatment with NASHA/Dx gel. For example, only 6/179 patients (3.4%) had proven pyelonephritis during long-term post-treatment follow-up over 7–12 years [Stenberg and Läckgren, 2007]. In another large cohort of patients ($n = 276$), albeit with a shorter follow-up period, UTIs after endoscopic treatment were reported in only three children (1%), although pyelonephritis was reported as a post-treatment complication in one case [Puri *et al.* 2007]. A third study showed that the mean incidence of UTIs, among those patients reporting any UTI, fell fivefold after endoscopic treatment, compared with the pre-treatment incidence (0.12 *versus* 0.68 UTIs/year, $p = 0.001$) [Wadie *et al.* 2007]. The overall reduction in UTI frequency was considerably greater (approximately 33-fold), as the percentage of patients experiencing UTIs reduced from 75 to 13%.

These results compare favourably with the incidence of UTIs following ureteral re-implantation or during antibiotic prophylaxis [Jodal *et al.* 1992; Weiss *et al.* 1992]. In the European arm of the International Reflux Study, after 5 years' follow-up febrile UTI was reported to occur in 33/150 patients (21%) managed conservatively, compared with 15/147 patients (10%) of children who underwent ureteral re-implantation [Jodal *et al.* 1992]. In the USA arm, febrile UTI was

observed in 15/68 children (22%) managed medically, and 5/64 children (8%) managed surgically [Weiss *et al.* 1992]. Moreover, a comparative study showed the rates of UTI and febrile UTI to be significantly lower among children successfully cured of VUR by endoscopic injection of NASHA/Dx gel than those cured by open surgery [Elmore *et al.* 2008].

Possible reasons for this apparent advantage with endoscopic treatment include the likelihood that it is effective for both VUR and bladder dysfunction [Läckgren *et al.* 2007], the fact that endoscopic treatment provides rapid cure of VUR, and the minimally invasive nature of the procedure. There is evidence that surgery may lead to long-term alteration of bladder motility patterns, and this may serve to increase the risk of UTI *versus* endoscopic treatment [Roihuvuo-Leskinen *et al.* 2007].

Management of VUR based on multifactorial assessment

Comparative appraisal of the treatment options for VUR has previously led to the conclusion that endoscopic treatment is the most favourable approach [Kirsch *et al.* 2006; Stenberg *et al.* 2002]. A treatment algorithm for VUR was proposed some years ago, with endoscopic treatment recommended as first-line active treatment for children with persistent reflux [Läckgren, 2003; Stenberg *et al.* 2002]. Open surgery was reserved for children failing endoscopic treatment, or considered to be at high risk of kidney damage (reflux grade V in children aged 1–10 years). Thus, only a small proportion of children with VUR would undergo open surgery. A very similar treatment strategy was advocated around the same time by other European authors [Capozza *et al.* 2003]. These recommendations are compatible with parental preference: in a survey, 80% of parents expressed a preference for endoscopic treatment, compared with 5% for antibiotic prophylaxis and 2% for open surgery [Capozza *et al.* 2003].

Treatment algorithms generally require patients to be classified for determining therapy and, in the case of VUR, reflux grade has been the primary means of classification. The VUR grading system is dependent on the extent of reflux and the degree of structural abnormality (ureteral dilation). This approach does not account for factors such as age, sex, renal scarring, bladder dysfunction, and whether reflux peaks during bladder filling or voiding. Such factors are now understood to

have significant bearing on the patient's prognosis, and a revised approach to the classification of VUR would be valuable. Indeed, 'it is ironic that we became so expert at surgically correcting VUR before understanding much of the natural history and true clinical significance of the condition' (John Woodard, personal communication). Based on today's knowledge, endoscopic treatment may be considered as first-line therapy for most children with persistent grade III–V reflux. Those with grade (II–) III–V reflux with scarred kidneys or ureteral anomalies such as double ureters are all candidates for early endoscopic treatment as the likelihood of resolution is very small in these patients. For reflux grade I–II and normal kidneys, often the only required treatment is short-term antibiotic treatment in case of UTI. Nevertheless, endoscopic treatment may also be an option among this group, particularly those with grade II reflux and renal scarring, bladder dysfunction or recurrent UTI – particularly older patients [Läckgren *et al.* 2007]. Children with grade III reflux and normal kidneys may be considered for initial, short-term antibiotic treatment and careful monitoring with yearly dimer-captosuccinic acid (DMSA) scans (those developing new infections should be re-assessed by VCUG and a DMSA scan). Open surgery is reserved for use only in the 10–15 % of children not responding to endoscopic treatment, and in patients with severe ureteral anomalies. In particular, refluxing primary megaureter is a contraindication because there is an increased risk of obstruction in these ureters [Snodgrass, 2004].

To support this approach, a new VUR classification system would be required, the aim being to ensure that we treat the patient and not the X-ray image from VCUG examination. There is a need to determine treatment not only according to reflux grade, but also renal scarring, bladder dysfunction, and whether reflux peaks during bladder filling or voiding. This is because the latter factors affect the risk of infection, risk of scarring and likelihood of resolution. Since bladder dysfunction is a potential cause of VUR, patients found to have bladder problems should first be offered therapy to correct this condition [Läckgren *et al.* 2007]. Children with VUR and bladder dysfunction persisting after approximately 6 months of urotherapy are considered eligible for endoscopic treatment [Läckgren *et al.* 2007]. Patients with renal scarring and/or bladder dysfunction may be considered as candidates for early intervention given the association

of these conditions with reduced VUR resolution rates. In all cases, there is a need for thorough discussion of the treatment options with the parents of children with VUR and, if they are old enough, the patient as well.

After endoscopic treatment, VCUG assessment is scheduled at 4–6 weeks and antibiotics are administered until that point. Provided that the treatment was shown to be successful by the first VCUG, the only follow-up would be a DMSA scan after 12 months and follow-up according to renal status and bladder function. Thus, little investigation of patients is required following successful endoscopic treatment. For patients diagnosed with VUR grades III–V at the 6-week VCUG, a second endoscopic treatment is recommended within 3 months, with antibiotic treatment continuing until then.

This proposed approach to managing children with VUR may be considered applicable in developing countries as well as the industrialized world. Poor access to antibiotics is common in developing countries; therefore patients not receiving early, curative treatment are vulnerable to recurrent, febrile infections. These are a burden on patients and their carers, while also potentially increasing the risk of renal damage. The low incidence of UTIs including febrile UTIs following endoscopic treatment decreases dependence on antibiotics, clearly favourable where their availability is poor.

Conclusion

VUR is associated with recurrent and febrile UTI as well as renal damage. The optimum approach to managing the condition remains controversial, but non-treatment appears inappropriate for most patients except those with reflux grade I–II and normal kidneys. Long-term antibiotic prophylaxis should not be considered viable as it does not protect against UTI and it encourages resistance among bacteria of the urinary tract. In contrast, endoscopic treatment provides a convenient means of curing the condition through a single procedure, without the need for major surgery. The cure rates with NASHA/Dx gel approach those seen with open surgery, and the post-treatment incidence of UTI is lower. Open surgery need only be undertaken in patients failing to respond to endoscopic treatment and in those with refluxing primary megaureter. A revised approach to the management of VUR may now be considered, with patients classified

according to several factors in addition to reflux grade. Further randomized, prospective studies are required to confirm the optimal management approach for VUR.

Conflict of interest statement

None declared.

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