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Review Article

Pediatric Urinary Tract Infections and Vesicoureteral Reflux: What Have We Learned?

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ABSTRACT

It has been nearly 50 years since Victor Politano and Wyland Leadbetter developed the first reliable operation for the surgical correction of vesicoureteral reflux (VUR). It dispelled the notion of bladder outlet obstruction as the primary cause of reflux. One might argue, however, since the operation was so reproducible that we learned too quickly how to correct VUR before truly understanding its pathophysiology and potential risk in children. There have been many controversies that have arisen lately regarding the management of reflux. These controversies include:

(1) The role of imaging in evaluating children with urinary tract infections (UTIs). More specifically, does every child need a voiding cystourethrogram (VCUG) and where does the DMSA scan fit into our evaluation?
(2) There is a growing concern for the use of long-term prophylactic antibiotics and we lack controlled studies that verify their usefulness.
(3) Where does the endoscopic correction of reflux fit into our armamentarium of managing children with reflux? Is it an alternative for antibiotic prophylaxis or is it an alternative for open surgical reimplantation?
(4) How do we truly establish the risk of reflux in a given child? We have traditionally assigned risk to the grade of reflux, however, are there other variables that may better define the true risk of renal damage in a child who has reflux and UTIs?

This paper explores each of these controversial areas to stimulate us to think more deeply about this common problem that we think we know so much about

Keywords : Urinary tract infection, vesicoureteral reflux, children

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INTRODUCTION

If there ever was a structural abnormality that defined a specialty, it would be that of VUR and pediatric urology. As Sir David Innis Williams once stated,

"The more that we looked for reflux the more often we found it.
This was the real launching point for pediatric urology.
Here we had a prospect of a surgical operation curing a common complaint"[1].

However, our initial thoughts about UTIs and VUR at that time were not quite accurate. In his address on receipt of the Pediatric Urology Medal from the American Academy of Pediatrics in 2003, Barry O'Donnell noted that there were several fallacies in our thinking, such as:

1. VUR is rare.
2. VUR is progressive.
3. The grading of reflux is not important.
4. Bladder outlet obstruction causes reflux.
5. VUR is always bilateral eventually.
6. VUR always causes progressive renal damage.[2]

In the ensuing 25 years we have encountered many controversies in our management of children with UTIs and reflux. What is the appropriate evaluation for a child with a UTI? Is an ultrasound (US) and VCUG still the standard of care or does nuclear scintigraphy have a role? Is antibiotic prophylaxis still appropriate for all children with VUR in light of growing concerns of individual and community based antibiotic resistance? Where does endoscopic treatment of reflux fit into our armamentarium for VUR management? And, finally what is the true risk of having VUR? Is risk related to grade or are there other factors that influence risk for renal damage in association with VUR? These questions continue to surface from time to time as we do not have definitive answers. This review article will address some of these controversies, although it is not likely to provide solutions.

EVALUATION OF CHILDREN WITH URINARY TRACT INFECTIONS

Several recent articles have questioned the routine use of US and VCUG for evaluating children with UTIs[3,4]. The study by Hoberman et al. concluded that US was not helpful in evaluating children with a febrile UTI in that it did not change the initial course of management[3]. Moorthy et al. concluded that in the context of a normal renal US examination, cystography contributes little to the management of children under one year of age with a UTI[4]. Our justification for evaluating children with UTIs has always been based on the following criteria:

1. The incidence of structural anomalies in children with UTIs is 30-50%, depending on the age group studied.
2. The recurrence rate of UTIs is approximately 30% within the first year in females.
3. Early data indicated that the incidence of renal scarring with pyelonephritis increases significantly after a second UTI.
4. In the pediatric population in particular it is hard to know for certain when that first UTI occurred, as many children are treated with antibiotics for febrile illnesses without having a urinalysis or a urine culture.

In addition, in the pediatric population clinical parameters are often unreliable to distinguish between pyelonephritis and cystitis. It is not unusual, therefore, to encounter a child as seen in Fig. 1 who presents with her first UTI at 9 years of age and a dimercaptosuccinic acid (DMSA) scan that shows multiple areas of scarring of the refluxing left kidney. In further conversations with the parents of this child it became clear that she had many febrile illnesses, the etiologies of which were undiagnosed.

Our justification for evaluation is based on excellent data such as that from Jodal and Lindberg indicating that, as the number

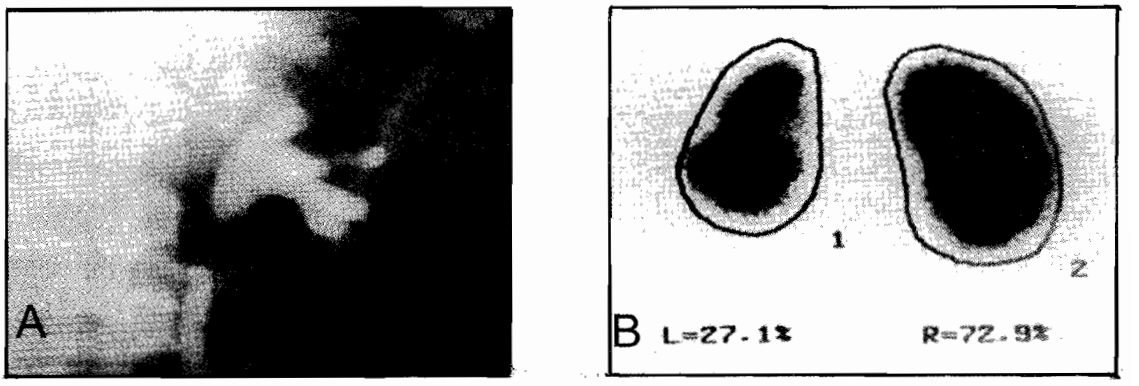

Fig 1: A 9 year-old girl with a history of a single febrile UTI and many prior undiagnosed febrile illnesses. **A.** VCUG demonstrating left VUR. **B.** DMSA demonstrated significant left renal scarring

of UTIs in an individual increases, the percent of renal scarring increases in a linear fashion[5]. Similarly, data from Stokland et al. indicate that the higher the grade of VUR the greater the risk of existing renal scarring at presentation[6]. We have also been influenced by the high percentage of children with renal scars who have VUR and the risk of developing hypertension in association with the presence of a renal scar[7]. There has also been some concern about the impact of VUR during child- bearing years as well (Martinell and Middleton studies)[8,9].

However, studies have continued to show that not all children with febrile UTIs have VUR. Majd et al. in their study of 94 children with febrile UTIs found that only two-thirds of their population had a positive DMSA scan indicative of acute pyelonephritis and of those with a positive DMSA scan only one-third had VUR[10]. The conclusion that one must reach, therefore, is that not all febrile UTIs are due to pyelonephritis and not all pyelonephritis is due to reflux. More recent data by Ataei et al. looked at 52 children with febrile UTIs over 5 years of age[11]. These children were studied with an acute DMSA scan and an US and early VCUG at 5 -7 days after presentation. They found that the distribution of children with and without reflux based on the DMSA scan was identical. In other words, the chance of having an abnormal DMSA scan was independent of the presence or absence of reflux. Regarding the Moorthy study previously quoted, these investigators looked at 108 children with UTI[4]. All children had normal ultrasounds. There were 8 children (3.7%) who had a late positive DMSA scan (≥ 1 year post infection), indicating a renal scar. Interestingly, half of those children with a late scar had no VUR on initial evaluation. Of those children with VUR (11.6%), only 16% of refluxing kidneys had evidence of renal scarring. The authors concluded that reflux does not necessarily identify an at risk population for renal scarring.

One must ask, therefore, what if the VCUG was reserved for only those children with a positive DMSA scan at initial presentation of a UTI? Would we miss a significant population of children who had reflux? Rosenberg et al. studied 65 children with febrile UTI with an acute DMSA, US and VCUG and a late DMSA scan at 6 months after infection[12]. About half of their children had an acute DMSA that was positive indicating acute pyelonephritis, while only 11% had a scar evident on the late DMSA scan. Twenty-four percent of their children had VUR. Ninety percent of those who had VUR had a positive DMSA scan. The one who did not have a positive DMSA scan had hydronephrosis on the US. The authors concluded that the US and DMSA scan identified all children who had VUR. Similarly, Hansson et al. studied over 303 children with febrile UTIs[13]. These

children had a DMSA scan and VCUG acutely and then again at 1 to 2 years later. Half of the children had a positive DMSA scan indicative of pyelonephritis. Of those children with a positive DMSA scan only half had VUR. Of those children with a negative DMSA scan, 5.4% had VUR, mostly grade I to II. On follow-up of the 7 who had grade III VUR with a negative DMSA scan, only 1 had evidence of renal scarring on a late DMSA scan, in 5 out of 7 the reflux resolved one year later, and 1 of these patients had recurrent UTI. These data have been substantiated by a work in progress by Manzoni et al. on 147 patients[14]. The conclusion from these data is that if one performed a VCUG only in children with a positive DMSA scan at the time of their infection, one would miss 10% of children with VUR, and two-thirds of that reflux would be low grade. Refluxers with moderate-grade reflux would have a low risk for renal scarring, a high rate of spontaneous resolution, and few recurrent infections. Similarly, Taskinen and Ronnholm studied 64 children with febrile UTIs, evaluating them with an US, acute DMSA, VCUG and late DMSA scan 2 years later and found a 20% incidence of scarring on the late DMSA scan[15]. However, of this group with a scar on a late DMSA scan, 9/12 had no evidence of VUR. Similar to the Moorthy data, therefore, this study implies that the VUR as an independent variable does not necessarily predict a group at risk for late renal scarring.

In conclusion, therefore, of children with febrile UTIs approximately half have a positive acute DMSA scan indicative of pyelonephritis. Out of those children with a positive DMSA scan, 30-40% will demonstrate VUR. Conversely, 90% of children with VUR will have had a positive DMSA scan indicative of acute pyelonephritis. Therefore, one would miss 10% of refluxers if one reserved a VCUG for a child with a febrile UTI and a positive acute DMSA scan, presence of hydronephrosis, or a dilated ureter. Most of the missed VUR would be low grade with a low risk for recurrent UTIs and late renal scarring.

PROPHYLACTIC ANTIBIOTICS

Prophylactic antibiotics first gained popularity 4 decades ago when Smellie and colleagues showed that the recurrence of UTIs can be reduced in children with VUR[16]. In a randomized trial of 48 children with UTIs, Smellie et al. demonstrated that in those children on prophylactic antibiotics there were no breakthrough UTIs compared to 11 UTIs in those children on no prophylaxis[17]. Those data are compatible with those of Lenaghan et al. which demonstrated that in children with recurrent UTIs, the use of antibiotics intermittently for treatment of an acute UTI, as opposed to prophylactic antibiotics, resulted in a 21% incidence of renal scarring[18]. One needs to recall that these data were accumulated at a time when corrective surgery for VUR was in its infancy and had a much higher complication rate than today. Therefore, correlation of high VUR grades with more frequent UTIs and an increased risk of renal scarring led to the common use of prophylactic antibiotics in the treatment of VUR[5,6]. Although low grades of VUR have a high spontaneous resolution rate, prophylactic antibiotics have been found to protect the kidneys from scarring. Given these findings, prophylactic antibiotics empirically became routine therapy for most children with primary VUR except for those with the highest grades. However, questions regarding the efficacy of prophylactic treatment, patient non-compliance, and the development of antibiotic resistance forces today's clinicians to re-examine the use of this common treatment practice[19]. This is especially necessary as there are few controlled, randomized studies assessing the efficacy of antibiotic prophylaxis in children with VUR.

Despite more than 40 years of experience with prophylactic antibiotics in the management of children with VUR, there is

a lack of controlled studies that address their role and efficacy. A meta-analysis of clinical studies indicated that 30-50% of VUR patients receiving prophylactic antibiotics will have a UTI within 5 years[20]. A direct clinical comparison of prophylactic antibiotics versus no prophylactic antibiotics showed similar 1-year UTI rates, which were 23.6% for children with grades I-III VUR receiving prophylactic antibiotics and 22.4% for those without prophylactic therapy[21]. In addition, Sjöström et al. reported that with prophylactic antibiotics, breakthrough UTIs were seen in 47% of high-grade infantile VUR patients[22]. When these findings are put in perspective with results from clinical studies comparing antibiotics to no antibiotics, one tends to conclude that prophylactic antibiotics may not be effective long-term in preventing UTIs in children.

Evidence also places into question the ability of prophylactic antibiotics to reduce or limit renal scarring. Reddy and colleagues found no differences in renal damage among VUR patients randomized to receive either antibiotic prophylaxis or no antibiotic[23]. In addition, Smellie et al. conducted a prospective study to examine renal function associated with VUR in 52 patients aged 1-12 years. Patients were randomized to either medical or surgical management[24]. Results indicated no difference at 4 years in renal function as measured by the percent change in glomerular filtration rate. In contrast, Garin et al. found a higher rate of pyelonephritis among patients with VUR who were treated with prophylactic antibiotics compared to those without prophylactic antibiotics, 12.9% versus 1.7%[21]. These findings raise significant concern about the standard practice of antibiotic prophylaxis for VUR. The questionable use of antibiotics is not just limited to the treatment of VUR. In a randomized trial, Clarke et al. reported that children with spina bifida on clean intermittent catheterization (CIC) and daily prophylactic antibiotics were more likely to have a symptomatic UTI than those on CIC without antibiotics[25]. In addition, the infecting organisms for those children on prophylactic antibiotics were resistant to the prophylactic antimicrobial.

Clinicians have reported that the reason for over-prescribing antibiotics among all infections is because of unrealistic patient expectations and insufficient time to discuss the rationale for antibiotic therapy with the patient[26]. Furthermore, patient expectations can influence physicians to prescribe antibiotic therapy even in the absence of appropriate indications for use[27]. Other factors influencing physician overutilization include diagnostic uncertainty, prescribing broad-spectrum agents when a narrow-spectrum agent would be more appropriate, lack of knowledge regarding optimal diagnostic approaches, lack of patient follow-up opportunities, and possible litigation concerns. Although all of these factors may not be the utilization driver within a VUR population, the potential similarities in factors may suggest the need for the education of parents and the re-education of clinicians regarding the role of antibiotic therapy in children with VUR.

In a review by Conway et al. of children with UTIs from a network of 27 primary care pediatric practices, it was found that antibiotic prophylaxis was not associated with decreased risks of recurrent UTI, but a signifi cant risk factor for anti-microbial resistance among children with recurrent UTI[28]. Many studies have confirmed that the increased use of antibiotics in individuals raises the risk for resistance in urinary tract pathogens as well as in normal bacterial flora[26,29,30]. For patients who are susceptible to UTIs, trimethoprim-sulfamethoxazole, nitrofurantoin, and beta-lactams are commonly given as first-line therapy. However, at present, the activity of these drugs against pathogens that are commonly associated with UTIs is poor, due to the widespread use of these agents[29]. Data suggest that 70% of *Escherichia coli* isolates can be expected to be resistant to ampicillin, 49% to a first-generation cephalosporin, and 37% to trimethoprim-sulfamethoxazole[31]. For other common pathogens, antibiotic resistance is also rapidly increasing. During the past five years, resistance to penicillin has increased by 300% and for agents such

as cefotaxime by over 1000%. Research has indicated an increase in vancomycin-resistant enteroccoci (VRE) colonization[32]. This finding is validated by Low et al. who found that the second most common occurrence of VRE is within the urinary tract[33].

Given these trends, clinicians must consider the value of initiating antibiotic therapy in light of this growing risk, a risk classified by the Infectious Disease Society of America and the World Health Organization as one of the world's most pressing public health problems[30,34]. The need for prophylactic antibiotic therapy must carefully consider the threat of, and the likelihood to prevent, subsequent infections. The importance of this concept cannot be overemphasized, as prior exposure to an antibiotic enhances the risk for development of a drug-resistant uropathogen[30,35-37]. Allen and colleagues found that children exposed to more than 4 weeks of antibiotics in a 6-month period were 23 times more likely to have an *E. coli* urinary isolate that was resistant to trimethoprim-sulfamethoxazole when compared with children who had received no antibiotics[38]. This information, along with data from Panaretto et al. confirms that current resistance patterns to trimethoprim and sulfonamides are increasing in children on prophylactic antibiotics[39]. Therefore, the prophylactic use of antibiotics should be reserved for conditions where the value of treatment is proven and outweighs potential risks.

In addition, there are data raising concerns about patient compliance with prophylaxis and its effect on developing antibiotic resistance. In one of the largest studies of VUR patients, Hensle et al. showed that only 17% of patients were at least 80% compliant with prophylactic therapy[40]. An earlier study showed that 97% of parents reported giving the antibiotic daily, but only 69% of urine tests were positive for antibacterial substances[41]. Additionally, compliance with long-term antibiotic administration has been shown to decrease dramatically by the first-year follow-up visit[39]. In a group of children with VUR without recurrent UTI, 84% of parents reported that their children were taking the prescribed antibiotics at 6 months, but only 28% had a therapeutic antibacterial activity in urine screening samples. Studies have shown that inadequate levels of antibiotics in the urine may be a factor in resistance patterns. In a study evaluating various urinary tract prophylaxis regimens, only two-thirds of the time was there a desirable concentration of a drug in the urine when assayed in the morning, during the day and before bedtime[41]. The undesirable antibiotic concentrations in the urine may result from the lack of compliance with the prescribed regimens, increasing the risk of break through infections. This effect may also partially explain the high rates of UTIs seen in some studies[39,41]. Not surprisingly, non-compliance with treatment regimens may further hasten the development of antibiotic resistance, as bacterial resistance is more likely to develop when patients are non-adherent to their antibiotic therapy[29,42].

Several studies have indicated that under certain circumstances, it may be safe to discontinue antibiotics in children with VUR[43-46]. While these studies are not randomized, each found a low risk of upper tract UTIs and a low risk for the development of renal scarring in older toilet trained children with VUR not on antibiotics. In a recent study by Georgaki-Angelaki et al. children who had been on antibiotic prophylaxis for 2 years and UTI free were randomized to continued prophylaxis or no prophylaxis, with a follow-up of 4 years[46]. There was no difference between the two groups in the incidence of UTI nor the resolution rate of VUR. There was no new renal scarring in either group as determined by DMSA scan.

VESICOURETERAL REFLUX RISK

Concerns regarding the safety and compliance of long-term antibiotic prophylaxis as well as parental concern regarding the trauma of repeated VCUG, along with the availability of a minimally

invasive approach to the correction of reflux has led to an increase in correction of VUR[47]. However, it may be more beneficial to identify children with VUR who are at high risk for renal damage and treat them differently than those who are at low risk for renal damage. In fact, many children with VUR have a benign course with little risk for upper tract damage.

From the philosophical theories of Galen, the anatomical dissections and drawings of Da Vinci, and the work on the precise physiology of the ureterovesical junction by gynecologist John Sampson, we learned that primary VUR is due to an abnormality of the vesicoureteral junction in which there is poor muscle backing of the ureter relative to intravesical pressures[48]. Our first approach to the correction of reflux was directed towards the bladder outlet, as it was thought that bladder outlet resistance was the likely cause of back-flow from the bladder to the kidneys. The experimental and clinical work by Politano and Leadbetter proved that primary reflux is due to an abnormality of the ureterovesical junction, and correction of the ureterovesical junction can be achieved with a reliable surgical procedure with a high success rate in eliminating reflux[49]. It was only later that we realized that other structural and functional abnormalities of the urinary tract can contribute to reflux. In some cases the causes are very obvious, such as seen with posterior urethral valves, neuropathic bladder, or ureterocele, but others are more subtle and it took a while for us to appreciate their contributions. These were primarily the category of patients with dysfunctional voiding whose bladder dynamics in some way contribute to VUR. Naseer and Steinhardt demonstrated that of the population of patients with reflux, 2.1% developed new renal scarring on antibiotic prophylaxis[50]. It was determined that 77% of the children who developed new renal scarring had symptoms or radiographic findings consistent with dysfunctional voiding. Similarly, Noe found that the majority of patients who failed standard ureteral reimplantation surgery also could be categorized as having some element of dysfunctional elimination syndrome[51]. Studies by Koff, Snodgrass and Hjalmas have shown a strong association between VUR and dysfunctional voiding and that dysfunctional voiding increases the degree of reflux, reduces the success of surgical correction, and reduces the chances of spontaneous resolution[52-54]. The European Arm of the International Reflux Study identified 18% of their population of children with VUR who had an element of bladder-urethral dysfunction[55]. These children were noted to have a higher risk of recurrent UTIs, an increased persistence of VUR, and an increased variability in the grade of VUR from study to study. It is evident, therefore, that children with VUR and dysfunctional voiding are a high risk group for recurrent UTIs, development of new renal scarring on antibiotic prophylaxis, and reduced spontaneous cessation of VUR. Studies such as that by Palmer et al. have shown that management of these children with antibiotic prophylaxis, timed voiding schedules, bowel management programs, and selective biofeedback results in an improvement in the reflux resolution rates[56]. However, one must accept that management of these children is time-consuming with significant issues such as compliance by the child and family with relapses quite common. Läckgren et al. have recently demonstrated that in a small population of children with VUR and evidence of bladder dysfunction, successful VUR correction with endoscopic injection of dextranomer microspheres resulted not only in a resolution of the reflux but also a significant improvement in symptoms of bladder dysfunction in 29 of 35 patients[57]. This raises some theoretical concerns about the relationship between VUR and bladder dysfunction.

Another population that appears different than the standard refluxer is a neonate with VUR. These are predominantly male children with high grades of VUR and a higher incidence of associated renal dysplasia. However, grade for grade, they appear to have a higher spontaneous resolution rate of VUR as well[58-60]. The urodynamic studies of these children have demonstrated a high incidence of abnormal bladder dynamics including bladder instability, incomplete contractions, uninhibited contractions, and an

Table 1: Characteristics of available injection materials modified from Russinko P and Tackett L.[68].

Product	Material composition	Particle size (μm)
Teflon, Polytef	Polytetrafluorethylene particles, which are inert and suspended in glycerin 50% by weight	4-100
Deflux	Dextranomer microspheres cross-linked in 1% sodium hyaluronan solution	80-120
Zyderm, Zyplast, Contigen	Derived from bovine dermis, cross-linked to glutaraldehyde; GAX 35; 35 mg/mL collagen; GAX 65; 65 mg/mL collagen suspended in pH neutral saline	-
Macroplastique	Polydimethylsiloxane, a biphasic copolymer polymerized and vulcanized polydimethylsiloxane in polyvinylpyrrolidone hydrogel	35-540; mean maximal diameter, 209 μm
Coaptite	Calcium hydroxylapatite spheres suspended in water and glycerin mixture with cellulose gel former	75-125
Urocol	50% microporous hydroxyl apatite ceramic suspended in gel with 4% collagen in glycerin	100-400
Chondrocytes	Auricular chondrocytes suspended in an alginate solution with calcium salt	20 x 106 chondrocytes/mL
Fat	Suprapubic adipose tissue obtained by microliposuction	-
Autologous collagen	Extracted from dermis	-
Autologous blood	Extracted from patient	-
Autologous bladder muscle	Extracted from animal	-

obstructed voiding pattern[61-63]. Additionally, accumulating data indicate that the status of the upper tracts at the time of diagnosis in this select population may be predictive of reflux outcome, both in terms of risk of renal damage and spontaneous resolution. Godley et al. showed that of infants with reflux, those with normal renal parenchyma had evidence of normal bladder function and a high rate of spontaneous resolution of their reflux, whereas those with abnormal renal parenchyma were proportionally more likely to have abnormal bladder function and a lower spontaneous reflux resolution rate[64]. Corroborating data by Mingin et al. have shown that neonatal refluxers with an abnormal DMSA scan had a high incidence of breakthrough UTIs (17/21) and a low rate of spontaneous resolution of reflux (0/27) compared with those with a normal DMSA scan (1/36 breakthrough UTIs, 19/36 VUR improved)[65]. One would conclude from these data that neonates with high-grade reflux who have abnormal renal parenchyma at birth have a high risk for breakthrough UTIs and, therefore, further renal damage and a low risk for spontaneous resolution of reflux.

Table 2: Meta-analysis of studies of endoscopic injection for VUR. (Elder et al.[69])

	Success Rate
1st Injection	72%
Deflux System	50%
Neuropathic Bladder	62%
Post-Reimplantation	61%

This neonatal reflux information appears to complement what we know about reflux and pregnancy. In a study by Martinell et al. it appeared that the presence of renal scarring at the time of pregnancy is a clear indicator of a high-risk pregnancy as opposed to the presence or absence of VUR[8]. Data by Mansfield et al. showed that those children who were successfully treated for reflux and later went on to have pregnancies were at higher risk for problems during pregnancy[9]. While this particular study may be difficult to interpret, one interpretation would be that those who were treated for reflux in childhood likely were a group of patients with a higher intrinsic predisposition to UTIs and renal damage. Similarly, the conclusion of Bukowski et al. is that reflux should be corrected prior to pregnancy when renal scarring is present[66].

One could conclude from the data in neonates as well as those from pregnancies, that VUR as an independent variable may not predict risk of renal damage or high-risk pregnancy, but rather the status of the renal parenchyma, i.e., scarring or dysplasia, is the more sensitive indicator.

ENDOSCOPIC CORRECTION OF REFLUX

The technique of endoscopic correction of reflux was first reported by Matouschek in 1981 using polytetrafluoroethylene[67]. Puri and O'Donnell then brought this clinical concept to the laboratory and demonstrated successful correction of experimentally produced VUR in a piglet model by the intravesical injection of polytetrafluoroethylene (PTFE)[68,69]. While many different materials have been used over the years (Table 1), dextranomer microspheres crossed-linked in 1% sodium hyaluronan solution (Dx/HA) is currently the most popular.

The effectiveness of endoscopic correction was reported in a recent meta-analysis by Elder et al. (Table 2)[71]. This study demonstrated a success rate of 72% for primary reflux with a single injection. Other studies have recently reported higher success rates with initial injection, which is likely the result of variations of the technique as well as user experience[72,73]. Long-term studies by Stenberg and Lackgren have indicated approximately 13% incidence of recurrence of VUR in those patients who present with recurrent infections[74]. Studies by Yucel et al. and Higham-Kessler et al. have shown that the success of the injection procedure appears to be related to the subjective appearance of a satisfactory mound creation at the time of the injection as well as the grade of reflux[75,76].

Since the technology has proven itself effective and dextranomer microspheres have been shown to be a safe material, the question that remains to be answered is: where does this technology fit into our armamentarium for dealing with children with reflux? Does this technology represent an alternative to open ureteral reimplantation or does it represent an alternative to long-term antibiotic prophylaxis? The answer to this question must await the results of controlled trials. Initial reports have demonstrated, however, that the endoscopic correction of reflux results in lower risk of UTIs in

patients with VUR compared with long-term antibiotic prophylaxis[77]. In a matched study, 114 patients received antibiotic prophylaxis and 13 underwent endoscopic correction with Dx/HA. The average number of UTIs per year was 0.28 in the antibiotic cohort and 0.08 in the Dx/HA cohort. While this was not a randomized trial, the implication here is that correction of VUR with Dx/HA injection resulted in significantly fewer UTIs compared to antibiotic prophylaxis in children with VUR[78].

CONCLUSION

Treatment algorithms for the management of children with VUR are steeped in tradition with very few randomized, controlled trials. It is important that we periodically re-evaluate our traditional protocols with new emerging clinical data, which would allow to appropriately place newer treatment modalities into our armamentarium for treating VUR in children. We look forward to the results of randomized controlled trials.

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