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The Changing Concepts of Vesicoureteral Reflux in Children

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Editorial

The Changing Concepts of Vesicoureteral Reflux in Children

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Over the past two decades, tremendous progress has been made in the diagnosis, management, and treatment of vesicoureteral reflux (VUR), thus changing our understanding of this entity from being surgical to medical disease.

VUR is most often identified following investigation for other urinary tract problems such as urinary tract infection (UTI) and prenatal hydronephrosis or in evaluation of a family history of VUR. The prevalence of VUR ranges from 0.4% to 1.8% of asymptomatic children but increases to 30–50% in children with a history of a febrile UTI. VUR in the presence of a UTI can lead to pyelonephritis and renal injury with permanent scarring (reflux nephropathy). Reflux nephropathy remains an important cause of renal failure in children and the subsequent need for renal transplantation in the United States. Furthermore, it is evident that VUR may be a component of dysfunctional lower urinary tract (i.e., dysfunctional elimination syndrome) and thus has further enhanced our understanding of this entity.

Since VUR may resolve spontaneously in the majority of patients without requiring surgical intervention, children with VUR are traditionally managed with antibiotic prophylaxis with the primary goal of preventing the long-term complications associated with VUR such as renal scarring, hypertension, and renal insufficiency/failure by the prevention of urinary tract infection. However, surgical correction may be required if there is a break-through UTI or failure to resolve after a period of observation. More recently, the management and rationale for the treatment of VUR have been re-evaluated. The risks and benefits of diagnosing VUR are being questioned from a health impact and financial level. For instance, the efficiency of prophylactic antibiotic in the management of VUR is being challenged. Furthermore, alternative and less invasive methods of treating VUR are being proposed with undefined long-term outcomes. Consequently, many controversies now exist for the management of VUR.

In this special issue, we have assembled 23 articles addressing the controversies associated with the diagnosis, management, and treatment of VUR. We hope to provide some understanding of what we know and do not know about VUR and stimulate scientific evaluations of VUR and its management.

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Review Article

Vesicoureteral Reflux: Where Have We Been, Where Are We Now, and Where Are We Going?

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Recommended by Walid A. Farhat

We present a retrospective review of the scientific and clinical advances, extending over four decades, which have linked vesicoureteral reflux, with renal injury, and urinary tract infection. We have traced the original studies, coupled with advances in technology which led to the awareness, and ability to detect and diagnose the problems early in childhood. These advances progressed through clinical studies which defined the epidemiology of both reflux and urinary tract infection. Along with these diagnostic advances, there were numerous surgical developments, which allowed progressive improvements in the outcomes and effectiveness of a variety of treatment modalities. All of this literature leads us to the current era, when several clinical trials are currently underway in an effort to more fully define the most efficacious and safe methods to treat vesicoureteral reflux and associated urinary tract infection.

Vesicoureteral reflux may have been the major catalyst for the development of the subspecialty of pediatric urology, now approaching a milestone in North America, with the soon-to-be awarding of a certificate of special competence. How did this happen?

In the first textbook of Urology in Childhood, 1974, Dr. Innes Williams included a chapter on reflux, in which his opening sentence states "the problem of reflux has occasioned more controversy than any other topic in pediatric urology" [1]. I submit in writing this article the view that this situation has changed very little to this day, more than 30 years later.

Reflux was recognized very early, as an abnormal function of the ureterovesical junction, but it was Hutch who recognized it in association with neurogenic bladder, in the spinal injured patients, and who linked the reflux to the renal injury in those patients [2]. Reflux was subsequently demonstrated in some pediatric patients with UTI, but there were several studies which showed that reflux was not present in normal infants. These data were brought forward because of the ready availability of voiding cystourethrography—we now assume that these studies are routine and customary—whereas in 1960s and 1970s they were neither available technically, nor did many imagers have any of the facilities or skills that are now standard of care throughout the world.

The next milestone was the recognition that vesicoureteral reflux was associated with urinary tract infections, but also that it occurred as a primary defect in children. Prior principles had shown reflux to be associated with other congenital anomalies or defects such as neurogenic bladder. Hodson and Edwards [3] described a relationship between urinary tract infections and reflux, and further investigators demonstrated this to be present in a significant number of children with recurrent pyelonephritis [4]. These findings led physicians and surgeons to recognize the importance of UTI as a cause of both pyelonephritis and as an extension of this to recognize relationship between chronic scarring and end-stage renal disease, and UTI with reflux. Kunin (1970) published data showing the prevalence of UTI in school-age children. The scene was set for the imposition of two forms of therapy which emerged as the science of the day—antibiotics for gram negative bacterial infections, and surgery for vesicoureteral reflux.

The 1970s witnessed the emergence of antibiotics, including aminioglycosides, chloramphenicol, and cephalosporins, which proved effective in the treatment of sepsis and pyelonephritis caused by gram negative organisms. Although one of these proved myelotoxic and was removed from use, the others continued to be employed more frequently, and further refinements both improved their

efficacy and reduced their toxicity. Along with the readily available treatment modalities, the recognition of UTI as an important cause of sepsis in the neonate and young infant became a more common diagnosis. In this era, the differential diagnosis fever in an infant included meningitis which was much more common as a cause of fever and sepsis in infants' than is now the case. Thus, the subsequent investigation of UTI, with personnel and equipment to carry out effective cystograms, led to the diagnosis of vesicoureteral reflux in increasing numbers. Parallel with the growing frequency of the diagnosis of reflux was a growing experience and expertise in the surgery of reflux. Politano and Leadbetter [5] described an effective operative procedure which could achieve successful treatment with relatively minimal morbidity—this became widely utilized in North America, while the Lich Gregoir extravesical techniques [6] were more widely used in Europe. Following upon these successes, Paquin [7], Glenn and Anderson [8], and finally Cohen [9] improvements and modifications of ureteroneocystostomy are resulting in their wide utilization throughout the world in 1980s. The AAP section of urology was started in this period, and the specialty of pediatric urology emerged as a recognized specialty, dedicated to the treatment of children with congenital defects of the genitourinary system.

Dr. John Duckett and a dedicated group of colleagues bridged the gap between pediatric urologists and pediatric nephrologists, in both Europe and North America, to formulate a prospective study to test the hypothesis of the best treatment for vesicoureteral reflux. The international reflux study was born and completed, with publications in 1992, which answered some questions, but left many more unanswered. It was apparent that surgical correction of reflux was feasible, safe, although inconsistent in the complication rates at varying centers. Similarly, it was apparent that reflux would resolve spontaneously. Thus, the most optimal treatment was uncertain. The outcomes measured were primarily renal scarring, but other features of the "disease" became more confusing—was the renal scarring pre-existent, or solely the result of the reflux, or of the UTI? Although dysfunctional voiding was an exclusion factor, the study concluded that 15% of children did have dysfunctional voiding. Was this now to play a part in the treatment of the recurring UTIs? Was the reflux actually a factor in the UTIs, since even after the correction of reflux, persistence of UTIs occurred? Many questions were answered, but many more remained.

In this era of excitement and involvement in the international reflux study, a new player emerged as O'Donnell and Puri [10] published data in 1984, showing that the cystoscopic injection of Teflon paste into the subureteric space could result in the resolution of vesicoureteral reflux. Following the rapid popularization of this technique, mainly in Europe, it was disclosed by researchers in USA [11] that Teflon could potentially be absorbed, and migrate to other areas of the body, including the brain and lymphatics. These data, combined with speculation and fear that leaked Teflon, leaked from prosthetic implants could be a potential cause of autoimmune disease, led the Federal authorities in USA to insure that the subureteric injection of Teflon would not be approved in North America. Nonetheless, a new debate had been born, centered on the child with UTI and vesicoureteral reflux. At meetings, becoming more populated with well trained and proficient pediatric urologists from around the world, debates became heated, stimulating, and amusing. Three of our greatest leaders, each a proponent of either open surgical correction, observational treatment alone or subureteric injection (Duckett, Ransley, O'Donnell), led the assemblies in ever increasing circles of confusion and varied convictions.

Two new pieces of data were added to the continuing puzzle; the emergence of antenatal ultrasound, which showed hydronephrosis in up to 1% of fetuses, and the publication by Noe [12], that vesicoureteral reflux could be shown in up to 25% of siblings who were diagnosed with reflux. The groups of children with reflux diagnosed on the basis of either antenatal hydronephrosis and subsequently diagnosed reflux (20% of those with hydronephrosis), and also those diagnosed on the basis of sibling screening led to an ever increasing population of children with reflux.

Perhaps the latest piece of the technology puzzle, was added by Läckgren et al., who published data on a newer substance, dextranomer/hyaluronic acid copolymer (Dx/HA) [13], which unlike other alternates to Teflon, proved to be durable, effective, and safe. It was approved for use in the USA and Canada and is now widely utilized around the world.

Antibiotic prophylaxis, the nonsurgical treatment modality used throughout all these decades as an alternate to surgical therapy, has now also come into dispute. The emergence of resistant strains of gram negative bacteria is growing, and possibly based on the widespread generic use of many antibiotics, a global increase in methicillin resistant staph aureus (MRSA) is posing serious challenges to treatment of infants with sepsis.

A new multicenter trial is now opened for recruitment in the United States and Canada (RIVUR), funded by the NIDDK, which will randomize children, presenting with UTI, and reflux between treatment with prophylactic antibiotics, and with observation alone [14]. The primary end point is the recurrence of UTI, with secondary end point being the development of renal scar. A similar study is ongoing in France.

We have come full circle, starting with a new diagnosis—reflux, previously unrecognized, which was assumed to be a cause of recurrent uti, and renal scarring, through three decades of evolving developments in technology and science showing a myriad of ways in which we could cure the reflux. Over 25 years ago, Dr. JR Woodard, a world leader of the time, stated "As one looks back over the last 30 years of reflux history, it is ironic that urologists have become so expert at its surgical correction before understanding much about its natural history and true clinical significance" [15]. We now dwell in a world where we STILL question whether the reflux itself is the major problem, or just an easily diagnosed and treated cofactor. Hopefully, the rigors of current science, based on prospective and randomized data, will answer some of these ongoing questions and allow us to treat the children,

whom we treat, with the best, safest, most cost-effective, and noninvasive methodologies available to achieve our health-related aims. I believe these aims continue to be the effective treatment and prevention of UTI and the prevention of renal injury.

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Review Article

Vesicoureteral Reflux, Reflux Nephropathy, and End-Stage Renal Disease

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Objective. To review the contribution of vesicoureteral reflux and reflux nephropathy to end-stage renal disease. *Data Source*. Published research articles and publicly available registries. *Results*. Vesicoureteral reflux (VUR) is commonly identified in pediatric patients and can be associated with reflux nephropathy (RN), chronic kidney disease (CKD), and rarely end-stage renal disease (ESRD). Patients with reduced GFR, bilateral disease, grade V VUR, proteinuria, and hypertension are more likely to progress to CKD and ESRD. Because progression to ESRD is rare in VUR and often requires many decades to develop, there are limited prospective, randomized, controlled trials available to direct therapy to prevent progression to ESRD. *Conclusions*. Identification of patients with increased risk of progression to CKD and ESRD should be the goal of clinical, biochemical, and radiological evaluation of patients with VUR. Treatment of patients with VUR should be directed at preventing new renal injury and preserving renal function.

1. INTRODUCTION

Vesicoureteral reflux (VUR) is a common finding in pediatric patients. Approximately 1/3 of patients who have had a urinary tract infection (UTI) have VUR and 9–20% of patients with prenatal hydronephrosis have VUR when tested postnatally [1]. The prevalence of VUR in the general pediatric population has been estimated recently to be as high as 17.2% [1, 2]. Some patients with VUR develop reflux nephropathy (RN), some patients with RN develop chronic kidney disease (CKD), and a small number of patients progress to end-stage renal disease (ESRD). While UTI and VUR are relatively common, ESRD is rare in the pediatric population with an unadjusted incident rate of 14.8 per million patients per year in 2005 for ages 0–18 years [3]. The goal of this article is to describe the contribution of VUR to ESRD in pediatric patients, define risks for progression, and review data indicating what treatments may prevent progression to ESRD for patients with VUR.

2. RENAL PATHOPHYSIOLOGY IN REFLUX NEPHROPATHY

The mechanisms for the development of ESRD in VUR are complex. In animals, when the flow of urine is obstructed in the developing kidney a series of abnormalities occur including (1) arrest of glomerular maturation, (2) glomerulosclerosis, (3) ischemia and necrosis of some tubular cells, (4) apoptosis of other tubular and collecting duct cells, (5) interstitial inflammation, proliferation, and fibrosis, and (6) tubular dilatation and atrophy [4–6]. In addition, in animals and humans there is evidence that scarring occurs in compound papillae where intrarenal reflux is present [7]. In humans, RN is usually identified as renal scarring as defined on dimercaptosuccinic acid (DMSA) scan in a patient known to have VUR. It is important to note that the causality is not completely clear as some patients have renal scarring by DMSA scan but do not have VUR. It is also clear that pyelonephritis in the presence of VUR may lead to new scarring on DMSA scans; however, some patients with VUR have RN with renal scarring by DMSA scan at the time of diagnosis whether or not they have had a urinary tract infection. This is highlighted by the fact that some patients diagnosed at birth have renal scarring as defined by DMSA scan [8, 9]. One possible explanation for this is that damage to the kidney may occur embryonically due to VUR. Alternatively, some of the genes that control normal development of the ureters and ureterovesicular junction also control renal development. Thus VUR may be associated

with either macroscopically abnormal renal development or subtle developmental changes that predispose the kidney to developing scarring as identified by DMSA scan. A portion of the patients who develop ESRD related to RN may have abnormally developed kidneys that progressively worsen over time with further decrease in renal function exacerbated by proteinuria, hypertension, and episodes of pyelonephritis. This is highlighted by the fact that in multiple studies, correction of VUR does not completely prevent the formation of new scars [10, 11], indicating that there may be worsening renal pathology even once VUR has been corrected in some patients.

3. REFLUX NEPHROPATHY IS A MAJOR CAUSE OF ESRD IN CHILDREN

Multiple registries in the United States and internationally have identified RN as an important cause of ESRD. For adults, RN is not a very common cause of ESRD in children. In the USRDS database, RN is not specifically listed as an etiology for ESRD; however, obstructive uropathy not due to ureteropelvic junction or ureterovesicular junction obstruction is one of the less common causes for ESRD. For all ages, obstructive uropathy accounted for 0.6% of the point prevalent cases for 2005 [3]; whereas diabetes accounted for 36%. The incidence of obstructive uropathy in the USRDS has been stable at approximately 0.3% since 1994 [12], but has increased from 0.1% for all ages for 1989–93 [13] to 0.3% for the time periods 1994–98 [12], and 1999–2003 [3]. In the north American pediatric population, RN is reported as the 4th leading cause for dialysis and transplantation with 5.3% of transplant patients having a diagnosis of RN and 3.5% of dialysis patients having a diagnosis of RN [14]. The incidence of RN in the pediatric population has remained stable from 2003 to 2007 [14, 15]. It is important to note that the 2nd and 3rd leading causes for dialysis and transplantation in children are obstructive uropathy and aplasia/hypoplasia/dysplasia either of which can be intertwined with RN [14]. Furthermore, in this pediatric population another 2.6% of the transplant patients and 2% of dialysis patients carry a diagnosis of prune belly syndrome which is a disease of urinary obstruction in uteroand is often associated with VUR [14]. The accuracy of these registries is dependent on those entering data and diagnostic codes and thus may overrepresent or underrepresent the importance of RN in ESRD. However, in various international reports reflux nephropathy either alone or in combination with congenital obstructive disease also is identified consistently as a leading cause of ESRD [16–21].

4. VUR IS COMMON IN CHILDREN; HOWEVER, ESRD RELATED TO VUR IS RARE

In the North American Pediatric Renal Trials and Collaborative Studies registry, RN accounts for approximately 5% of the pediatric ESRD population [14]. It is possible to dispute the accuracy of this figure as this registry depends on voluntary reporting of data and there is no verification of the accuracy of the assigned diagnoses. However, if one uses this figure as an estimate and combines it with the annual incidence of ESRD for ages 0–18 reported by the USRDS of 14.8 per million, then the incidence of ESRD related to RN in the pediatric population would be approximately 0.7 per million patients [3, 14]. If one compares this annual incidence to the estimated prevalence of VUR in the general population, which has been recently reported as 17.2% or 172 000 per million, it is clear that the vast majority of patients with VUR do not develop ESRD. Even if one uses older estimates of the prevalence of VUR in the general population of 1-2% or 10 000 to 20 000 per million patients [2, 22], VUR is much more common than ESRD. Since the most common type of VUR is low-grade VUR or grades I–III VUR, this implies that lower grade reflux very rarely is associated with decreased renal function. Given that most patients with VUR do not develop ESRD or even CKD, much work has centered on identifying those patients with VUR who are at risk of developing CKD and ESRD. This work has been complicated by the fact that many older reports on outcomes of VUR were based on datasets from referral centers, not the general pediatric population, and thus are likely to have a strong bias towards patients with more severe disease.

5. RISK FACTORS FOR PROGRESSION TO CKD AND ESRD IN PEDIATRIC PATIENTS WITH VUR

Multiple retrospective trials have identified factors predictive of progression to CKD and ESRD in pediatric patients with VUR (Table 1).

There have been few papers that have focused solely on progression to ESRD as a primary endpoint in patients with RN, since, as described above, ESRD in general is a rare event for patients with VUR. Table 1 lists studies describing risk factors for CKD and ESRD in patients with VUR. Ardissino et al. retrospectively evaluated the risk of progressing from CKD to ESRD in a cohort of 322 pediatric patients with VUR and creatinine clearance (CrCl) <1.25 mL/s per 1.73 m^2 body surface area and found an overall risk of 56% for progressing to ESRD by the age of 20 [21]. Not surprisingly, those patients with CrCl <0.67 mL/s per 1.73 m^2 had a 4-fold increased risk of progressing to ESRD compared to those with CrCl $\geq$ to 0.67 mL/s per 1.73 m^2. In addition, age at diagnosis was not associated with an increased risk of progression to ESRD with those diagnosed at age greater than 6 months having no significant difference in risk of progression to ESRD compared to those diagnosed at age $\leq$6 months. In this cohort, grade IV reflux was the most common grade of VUR; however, information on the grade of VUR was reported for only 51% of the patients, making it difficult to relate risk of progression to grade of reflux. 29.1% of the patients were either hypertensive or being treated with antihypertensive medication, demonstrating the association between hypertension and RN. In addition, 104 of the 322 patients were evaluated for proteinuria, and approximately 1/3 (34/104) had moderate to severe proteinuria (uPr/uCr 0.95–7.2). Those patients with moderate to severe proteinuria showed a statistically significant larger mean rate of CrCl decrease when compared to those with

Table 1: Characteristics of studies reporting CKD and ESRD data for VUR.

Study	N (males)	Mean length of F/U in years (range)	% with reflux >/= grade 3	Incidence of CKD (upper limit of GFR for CKD in mL/s per 1.73 m^2)	Incidence of ESRD	Predictors of ESRD/CKD
Ardissino, J Urol, 2004 [21]	322 (245)	>5	95%	N/A—CKD was an inclusion requirement	56%	Proteinuria, CrCl <0.67 mL/s/1.73 m^2
Caione, BJU Int, 2004 [23]	50 (42)	6.3 (1–16)	100%	54% (1.3)	0%	Creatinine r >53 umol/L in the first year
Neild, BMC Neph, 2004 [24]	44 (22)	NR	Not reported (NR)	N/A—CKD was an inclusion requirement	N/A	Proteinuria, GFR < CrCl <0.83 mL/s/1.73 m^2
Lahdes-Vasama, NDT, 2006 [25]	267 (58)	37 (27–48)	NR	67% (1.5)	9%	Bilateral scarring
Mor, BJU Int, 2003 [26]	100 (21)	20–30	NR	1% (1.5)	0	NR
Silva, Ped Neph, 2006 [27]	735 (208)	6.3 (0.5–34)	60% of renal units	3.1% (<1.25)	1.5%	Hypertension
Silva, Ped Neph, 2006 [28]	184 (69)	6.5 (1.1–34)	100%	15%	5.4%	Bilateral VUR, grade V VUR, diagnosis before 1990, diagnosis at age >24 months

mild or no proteinuria, thus demonstrating that proteinuria is associated with ongoing renal deterioration and may be a target for therapies to prevent progression to ESRD.

Because having CKD increases the risk of progressing to ESRD in patients with VUR, risk factors for progressing to CKD are highly likely to be significant predictors for the progression to ESRD. Several studies have focused on risk factors for developing CKD in patients with VUR. Silva published data on a retrospective cohort of 735 pediatric patients with VUR of all grades with 29% of the patients having high-grade VUR (grades IV and V) [27]. Thus, this cohort exhibited some selection bias as the rate of high-grade VUR was significantly higher than reported in studies in the general population. In this cohort, 3% developed CKD (as defined by GFR <1.25 mL/s per 1.73 m^2 body surface area as estimated by the Schwarz formula) and 1.5% developed ESRD (GFR <0.25 mL/s per 1.73 m^2). Progression to CKD was strongly associated with hypertension. As part of the same work, Silva et al. evaluated 184 pediatric patients with severe bilateral reflux (grades III–V) followed at a single tertiary care center [28]. Mean follow-up was 78.6 months. All patients received daily antibiotic prophylaxis and 15% (27/184) had surgical reimplantation. In this higher-risk cohort, the estimated probability of developing CKD was approximately 15% at 10 years postdiagnosis of VUR. In multivariate analysis, age at diagnosis >24 months, VUR grade V, and bilateral renal damage were associated with an increased risk for CKD. Interestingly, diagnosis of VUR after 1990 was associated with reduced risk for CKD. This data implies that our current diagnosis and treatment of VUR may reduce the risk of developing CKD. In addition, the estimated risk of CKD was 0% for patients with grade III reflux or a negative DMSA at the time of diagnosis. The lack of progression to CKD in those patients with a normal DMSA at diagnosis implies that, perhaps, it is only those kidneys with congenital lesions or that already have been significantly damaged at diagnosis that are at risk for development of significant renal impairment.

Several other studies also have focused on high-risk populations of VUR patients. Neild et al. evaluated a high-risk population of 44 patients with bilaterally scarred kidneys due to primary reflux or bladder dysfunction and GFR 0.25–1.0 mL/s per 1.73 m^2 based on either an eGFR using the Jelliffe formulae or plasma clearance of EDTA [24]. They identified a watershed GFR of 0.83 mL/s per 1.73 m^2 below which the likelihood of progressing to ESRD increased substantially. In addition, they identified proteinuria as predictive of increased risk of CKD and were able to demonstrate a protective effect of ACE inhibitors on the rate of decline of renal function for patients with eGFR > 0.75–0.83 mL/s per 1.73 m^2. Caione et al. retrospectively reviewed 50 patients from Italy with bilateral VUR grades III-V diagnosed in the first year of life with an average follow-up of 6.3 years [23]. In their cohort, 54% of the patients developed CKD as defined by eGFR <1.3 mL/s per 1.73 m^2. All were boys, and in multivariate analysis neither number of UTIs nor prenatal diagnosis modified the likelihood of CKD. In multivariate analysis, a serum creatinine >53 umol/L significantly increased the likelihood of developing CKD. These two studies, while both small, appear to demonstrate that there is a threshold after which renal function declines with much greater frequency to CKD. In addition, Caione's study did not identify an association of CKD with febrile UTIs, implying once again that, perhaps, patients with severe

VUR progress to CKD due to ongoing inflammation and pathologic changes or developmental abnormalities rather than acquired damage.

6. VERY LONG-TERM FOLLOW-UP OF VUR PATIENTS

There have been several other retrospective cohort studies from a variety of populations with very long follow-up that evaluated the long-term outcome of VUR. For these patients with very long follow-up, treatment was initiated in some as long as 40 years ago, and it is possible that current treatment protocols, including more aggressive treatment of voiding dysfunction, may yield different outcomes than treatment practices from 40 years ago. In addition, these cohorts from several decades ago also appear to share a selection bias towards patients with more severe VUR and higher rates of scarring, perhaps because only the most severe VUR with recurrent infections was diagnosed in the past. Also, renal scarring was identified by intravenous pyelogram which is not as sensitive as DMSA scans; thus, patients identified as having renal scarring had more severe renal damage. Lahdes-Vasama et al. evaluated a cohort of Finnish patients followed for an average of 37 years [25]. They attempted to enroll 267 patients with VUR diagnosed between 1955 and 1965 but only were able to report information on current renal function for 127 of the patients. In this cohort, 12/265 had died due to kidney-related conditions, 7/265 had undergone renal transplantation, and 1/265 was on hemodialysis. For those who agreed to enroll, 85/127 had GFR <1.5 mL/s per 1.73 m^2, 4/127 had GFR <60 mL/min/1.73 m^2, and 1/127 had GFR <0.50 mL/s per 1.73 m^2 based on the Cockcroft-Gault formula. Among the enrolled patients, 35% had unilateral scarring and 24% had bilateral scarring by ultrasound, and the patients with bilateral scarring were significantly more likely to have reduced GFR. Interestingly, this Finnish cohort had no increased prevalence of hypertension compared to the rest of the Finnish population. The study implies that approximately 7% of patients with VUR progress to ESRD; however, the study was limited because they were unable to evaluate grades of reflux or the presence or treatment of voiding dysfunction, and there was a very high rate of renal scarring that was severe enough to be measurable by ultrasound. These factors indicate that there may have been significant selection bias in this cohort.

El-Khatib et al. reported data from 293 patients who were diagnosed with RN or VUR between 1971 and 1986 in Australia [29]. In this group, most patients were females who presented with febrile UTI; there was no information on VUR grade; and 89% of the patients had renal scarring on IVP. Thus, this population was highly selected for patients with more severe RN than a general population of patients with VUR. In this cohort, 37% demonstrated deterioration in renal function based on rising serum creatinine. In multiple regression analysis, the independent risk factors for rise in serum creatinine were proteinuria, hypertension, elevated creatinine at presentation, bilateral VUR, and male sex. Zhang and Bailey presented retrospective data on 294 (59 males) patients over 15 years of age who had been followed on average for more than 10 years. At last follow-up, 24% had creatinine clearance <1.2 mL/s per 1.73 m^2 [30].

There have been several other smaller long-term follow-up studies published. Mor et al. reported data from 100 Israelis (79 women and 21 men) followed for more than 20 years post antireflux surgery [26]. In their cohort, only 1/100 patients had an abnormal serum creatinine level; however, eGFR was not reported, no information on voiding dysfunction was reported and there was no information on VUR grade. Given these limitations, this study indicates a low risk of progression to ESRD for their cohort. Arze et al. presented data from 130 patients (16 male) identified in 1976 as having renal scarring as defined by IVP or pathologic evaluation of renal tissue post nephrectomy [31]. In their cohort which was followed for up to 240 months, 18% had, or developed, CKD as defined by Cr >130 uM/L. Hypertension, proteinuria, and repeated UTI were associated with increased GFR. Nakashima et al. followed 95 patients who had renal scar or grade III or higher VUR and found that 3/995 developed ESRD and that 35% demonstrated renal function deterioration [32]. In their cohort, bilateral scarring, proteinuria >300 mg per day, diastolic hypertension, and low GFR (mean 0.82 mL/s per 1.73 m^2) were associated with increased risk of deterioration of renal function.

7. PREVENTION OF ESRD IN PATIENTS WITH VUR

Currently, there is little evidence from prospective, randomized controlled trials to direct therapies to prevent ESRD in patients with VUR. One goal of treatment is to try to prevent recurrent episodes of pyelonephritis and renal scarring by treating voiding dysfunction, surgically correcting VUR, using daily antibiotic prophylaxis and treating episodes of pyelonephritis quickly and effectively [33] (see Figure 1). All patients should be completely evaluated and treated for voiding dysfunction as part of the evaluation and treatment of VUR in order to maximize bladder function and preserve renal function. Randomized controlled trials that have tested the benefit of surgical correction of VUR or prophylactic antibiotic treatment have not demonstrated either is more efficacious in preventing renal scarring or the overall rate of recurrent UTIs [10, 11]. Critically, these studies did not have a control group that received only observation. In one of these trials, the International Reflux Study in Children trial, surgical correction of grades III and IV reflux did reduce the occurrence of febrile UTI. Unfortunately, this did not correspond to a decrease in new renal scars or an improvement in renal function in surgically treated children [10]. Several recent reports have questioned the utility of daily antibiotic prophylaxis [34–36]; however, it is important to note that the studies from Garin et al. [35] and [34] Conway et al. reported on few male subjects and did not address high-grade VUR. Specifically, the Garin trial excluded those with VUR grades IV and V, and the Conway study included only 10 patients with VUR grades IV and V. Another recent randomized prospective trial demonstrated a benefit of prophylactic antibiotics versus observation in preventing positive surveillance urine cultures in asymptomatic boys with grade III VUR [37]. In the near future, we will hopefully

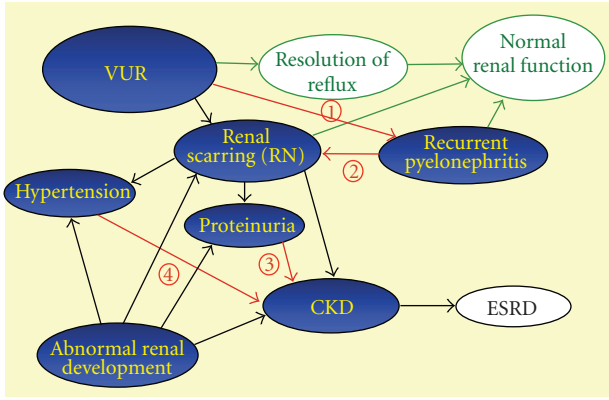

Figure 1: Schematic representation of factors involved in progression to ESRD for patients with VUR. In the majority of patients with VUR, VUR resolves and the patients demonstrate normal renal function (green pathway). Some patients with renal scarring and/or who have recurrent pyelonephritis also retain normal renal function (green arrows). Other patients with VUR develop RN, proteinuria, and hypertension. In all cases, abnormal renal development can accompany RN and contribute to renal scarring, proteinuria, hypertension, and progression to CKD (solid black arrows). Prevention of ESRD focuses on intervening to prevent recurrent pyelonephritis (1), by actively evaluating and treating episodes of pyelonephritis to prevent renal scarring (2), and by treating hypertension (3) and proteinuria (4) to preserve renal function.

have new data from a large, multicenter trial comparing daily antibiotic prophylaxis versus observation in patients with low-grade reflux [38]. At this point in time, there does not appear to be good evidence to support using daily antibiotic prophylaxis to prevent UTI or renal scarring in patients with VUR grades I–III; nor is there evidence that for grades III-IV VUR surgical correction of VUR prevents new renal scarring compared to daily antibiotic prophylaxis. Because grade V VUR is rare, there have not been any significant randomized, controlled, prospective trials to evaluate treatment options. Thus, the treatments that may prevent ESRD in this high-risk population are incompletely characterized. For patients with high risk of progression to CKD and ESRD such as those with grade IV and V reflux, significant renal scarring and those with reduced GFR, the surgical correction of reflux and daily antibiotic prophylaxis should be strongly considered; and risks and benefits of these treatments should be discussed with families. In addition, close clinical follow-up and rapid treatment of episodes of pyelonephritis should be instituted to preserve renal function and prevent progression to ESRD.

8. HYPERTENSION AND PROTEINURIA AS THERAPEUTIC TARGETS FOR PREVENTION OF ESRD

Another aspect of preventing the progression of RN to ESRD is the treatment of hypertension and proteinuria, both of which are indicators of renal damage and contribute to ongoing deterioration of renal function in many renal conditions. As described above, multiple studies have demonstrated a correlation between RN and hypertension. Hypertension has been shown to affect the rate of decline of renal function in other conditions, thus controlling hypertension should be a significant goal for treatment of patients with VUR.

In addition, multiple studies have demonstrated a correlation between proteinuria and risk for CKD in RN. The magnitude of proteinuria associated with increased risk of CKD or deterioration of function varies somewhat but even mild proteinuria appears to be associated with increased risk for renal deterioration. El-Khatib et al. showed an increased risk of deterioration of renal function for patients with >0.2 G per day of proteinuria with a progressively increasing risk of deterioration for patients with >1 G per day of proteinuria [29]. Nakashima et al. demonstrated an increased risk for deterioration of renal function for patients with >0.3 G/day of proteinuria [32]. Neild et al. also demonstrated a correlation between increased proteinuria and elevated creatinine with patients having a GFR of 0.25 mL/s per 1.73 m^2 to 0.5 mL/s per 1.73 m^2 having an average protein to creatinine ratio of 209 mg/mmol compared to 38 mg/mmol for those patients with GFR of 0.83 mL/s per 1.73 m^2 to 1.0 mL/s per 1.73 m^2 [24].

Neild et al. also presented the only data in VUR patients that ACE inhibitors may be able to slow the progression of renal deterioration associated with severe RN [24]. One caveat to their finding was that benefit of ACE inhibition was demonstrated only for those patients with mildly reduced GFR of 0.83 mL/s per 1.73 m^2 to 1.0 mL/s per 1.73 m^2 [24]. There is evidence that in nondiabetic patients with renal parenchymal abnormalities that ACE inhibition reduces proteinuria and may help to preserve renal function [39–41]. Given the benefit of ACE inhibition in other renal conditions and the limited, but promising, data presented by Neild et al. [24], ACE inhibitors and/or angiotensin receptor blocking agents should be the first choice for controlling hypertension and proteinuria and should be initiated early in the course of disease. Furthermore, based on data from other nondiabetic renal disease, one should use ACE inhibition and/or angiotensin receptor blockade even in the absence of hypertension when a patient has VUR and proteinuria. Controlling hypertension and proteinuria in patients with VUR should be considered standard maintenance therapy for those with VUR and RN.

9. CONCLUSIONS

VUR is commonly identified in pediatric patients and can be associated with reflux nephropathy, CKD, and, rarely, ESRD. The progression of RN to CKD and ESRD is more likely in patients with reduced GFR, bilateral VUR and/or renal scarring, grade V VUR, proteinuria, and hypertension. Identification of patients with these clinical characteristics should be the goal of clinical, biochemical, and radiological to evaluation of patients presenting with hydronephrosis on prenatal ultrasound or febrile UTI. Because progression to ESRD is rare in VUR and often requires many decades to develop, there are limited prospective, randomized, controlled trials available to direct therapy. All patients should

be evaluated and treated for voiding dysfunction, where appropriate, and rapidly diagnosed and treated for recurrent pyelonephritis. Evaluation and treatment of patients with VUR should be directed at preventing pyelonephritis and new renal injury; however, there is little evidence that either surgical correction of VUR or antibiotic prophylaxis prevents pyelonephritis and new renal scarring in comparison to careful clinical observation alone. In addition, for those patients who do develop RN, care should be taken to normalize blood pressure and reduce proteinuria in order to preserve renal function. In the future, with continued basic research, we may be able to develop pharmaceutical therapies aimed directly at the molecular pathophysiology of RN to slow progression of RN to ESRD. For now, we must provide the best supportive care to patients to preserve renal function and prevent ESRD in patients with vesicoureteral reflux and reflux nephropathy.

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Review Article

Bladder Dysfunction and Vesicoureteral Reflux

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In this overview the influence of functional bladder disturbances and of its treatment on the resolution of vesicoureteral reflux (VUR) in children is discussed. Historically both bladder dysfunction entities, the overactive bladder (OAB) and the dysfunctional voiding (DV), have been described in conjunction with VUR. Treatment of the dysfunction was also considered to influence spontaneous resolution in a positive way. During the last decades, however, papers have been published which could not support these results. Regarding the OAB, a prospective study with treatment of the bladder overactivity with anticholinergics, did not influence spontaneous resolution rate in children with a dysfunction including also the voiding phase, DV and DES (dysfunctional elimination syndrome), most studies indicate a negative influence on the resolution rate of VUR in children, both before and after the age for bladder control, both with and without treatment. However, a couple of uncontrolled studies indicate that there is a high short-term resolution rate after treatment with flow biofeedback. It should be emphasized that the voiding phase dysfunctions (DV and DES) are more severe than the genuine filling phase dysfunction (OAB), with an increased frequency of UTI and renal damage in the former groups. To be able to answer the question if treatment of bladder dysfunction influence the resolution rate of VUR in children, randomized controlled studies must be performed.

1. INTRODUCTION

There is a close relationship between bladder dysfunction and vesicoureteral reflux (VUR). This is most evident in children with neurogenic bladder dysfunction, in which the high intravesical pressure due to outflow obstruction induced by detrusor/sphincter dyssynergia is directly responsible for the development of the reflux. Another example of VUR as a secondary phenomenon is in boys with posterior urethral valves, where the reflux is secondary to an anatomical obstruction in the urethra. In most cases of secondary reflux, normalisation of bladder function means spontaneous resolution of the VUR.

When it comes to primary VUR, a close connection to bladder function pathology of nonneurogenic origin has also been established. Studies have been published describing children with functional bladder disturbance and VUR after toilet-training age. Studies from the 1980s most often dealt with girls who have overactive bladders (OAB) in combination with reflux, and treatment of the dysfunction positively influenced resolution of the reflux. During the last decades, however, bladder dysfunction including the voiding phase, such as dysfunctional voiding and dysfunctional elimination syndrome, has been reported to have a negative influence on VUR resolution in some studies. In other studies, treatment of the dysfunction has improved the resolution rate.

Children with high-grade congenital reflux have also been shown to have abnormal bladder function in about half of the cases. This dysfunction was characterised by an overdistended bladder and incomplete emptying. The dysfunction per se had a negative influence on spontaneous resolution of VUR, which did not improve despite treatment.

In this overview of bladder dysfunction and VUR, only primary reflux is discussed. There are some contradictory results in the literature available, as indicated above, which make an overview interesting. One of the major problems is the fact that the level of evidence in almost all papers is low, most have level three, a few have level two, and no paper was identified as level one.

2. STANDARDISATION OF TERMINOLOGY

When studying the literature about bladder dysfunction in refluxing children, one finds that there is still confusion emanating from differences in terminology (especially between the US and Europe), diagnostic procedures (urodynamic or clinical), degree of dysfunction, and so on. In this review, two bladder dysfunction entities are addressed in children after the age for bladder control: overactive bladder (OAB) and dysfunctional voiding (DV). The ICCS definitions of these entities are used. This means that dysfunctional voiding is only used in the sense of a dysfunction during the voiding phase, characterised by increased activity in the pelvic floor during voiding. The term can only be applied if repeat uroflow measurements show a staccato or interrupted pattern [1]. Dysfunction elimination syndrome (DES) is also discussed, and refers to an abnormal pattern of both bladder and bowel. It is characterised by withholding, often with incontinence. The bladder part of this syndrome can be recognised as dysfunctional voiding.

The overall term recommended in the standardisation document for bladder dysfunction is lower urinary tract (LUT) dysfunction. This term is used as a synonym for bladder dysfunction in the present overview.

3. BLADDER DYSFUNCTION CHARACTERISTICS IN CHILDREN WITH VUR

3.1. Before the age for bladder control

In the early 1990s, bladder dysfunction was reported in small infants with high-grade reflux. The dysfunction was characterised by low bladder capacity, high voiding pressure, and overactivity during filling [2–4]. Later studies have shown that both low capacity and high voiding pressure are normal findings in urodynamic investigations in this age group [5], while longitudinal studies of children with high-grade VUR diagnosed during infancy have shown a completely different bladder function pattern after the infant year; high capacity bladder with incomplete voiding [6, 7].

Dyscoordination at voiding was often seen in these young children with VUR, a finding that can be suggested as the reason for the high capacity bladder with incomplete emptying.

However, investigations of nonrefluxing children have shown that dyscoordination at voiding was seen in healthy infants, both in cystometric [5] and free voiding studies [8]. The free voiding studies are longitudinal investigations in healthy children and the finding was recognised as an immature phenomenon that was quite common early in infancy and then decreased and was not seen after the age for bladder control [8].

Interestingly, a bladder dysfunction pattern that was similar to the above-mentioned high capacity bladder with incomplete emptying dynamics was described as early as 1987 by Griffiths and Scholtmeijer [9] in urodynamic investigations of young children with VUR. They showed two distinct bladder patterns. The most common (about 50%) in the 104 VUR patients was characterised by urethral overactivity during voiding with relative weak voiding contractions, while detrusor overactivity during filling was not a major finding. This bladder pattern was seldom seen together with incontinence, but the reflux was often bilateral, combined with renal abnormalities and frequent UTIs, findings similar to what have been shown for the children, discussed above, with congenital high-grade VUR [6, 10]. The other bladder pattern, seen in about 25%, was urodynamically characterised by overactivity often seen together with bladder symptoms such as incontinence. The kidneys were often normal, the VUR often unilateral, and UTIs were seldom seen.

High-capacity bladder has also been reported in other studies in children with VUR after the infant year, especially in boys [11] and together with dilating VUR [11–13]. It has also been reported as a factor that is negatively correlated to spontaneous resolution of the reflux.

3.2. After the age for bladder control

Prevalence of LUT dysfunction in children with VUR

The reported prevalence of bladder dysfunction in a VUR population varies. When diagnosed using invasive urodynamic investigations, higher figures were generally found (38%–75%) in contrast to what was seen when nonurodynamic investigations were used (18%–52%) (Table 1). This variation was probably related to factors such as grade of VUR, age of the children, and, obviously, how the dysfunction was diagnosed.

The earliest studies of bladder dysfunction mostly dealt either with dysfunctional voiding or the overactive bladder. Recent studies often give the prevalence of both dysfunctions together in children with VUR. The advantages of separating the dysfunctions are that different treatment modalities can be evaluated, as well as differences in results when it comes to effects on VUR resolution. The disadvantage is that the dysfunctions often are combined and sometimes difficult to separate.

The first reports about bladder dysfunction and VUR came in the 1970s. Hinman and Baumann [22] and Allen [23] described a severe form of dysfunctional voiding that was suggested to cause the VUR in parallel to what was seen in neurogenic bladder dysfunction. The investigations indicated that the condition was rarely seen, but no prevalence figures were reported.

A few years later, Koff and Murtagh [18] and Taylor et al. [17] reported on OAB in conjunction with VUR, and they found high prevalence figures for the dysfunction (55–75%), mainly seen in girls after the age for bladder control. Koff and coworkers [18] also indicated that the reflux had a higher spontaneous resolution rate after treatment of the bladder problem with bladder regimen and anticholinergics, as compared with a group with similar grades of reflux but without overactivity in the bladder (Table 3). Other more recent studies (Table 1) showed a prevalence of OAB between 25% and 38% in urodynamic studies of children with VUR of different grades, whereas the prevalence in a nonurodynamic study was only 8% (Table 1).

Table 1: Prevalence of bladder dysfunction in patients with VUR.

Reference	Age (years)	Patients with VUR (number)	Bladder dysfunction (% of total)	Overactive bladder (% of total)	Dysfunctional voiding (% of total)	Dysfunctional elimination syndrome (% of total)
Nonurodynamic investigations						
Snodgrass 1991 [14]	0.1/16	39	20%			
Van Gool et al. 1992 [12]		310	18%	8%	6%	
Snodgrass 1998 [15]	3–10	128	52%			
Homayoon et al. 2005 [16]	>3.5–4	342	20%			
Urodynamic investigations						
Taylor et al. 1982 [17]	4–15	37	75%	75%		
Koff & Murtagh 1983 [18]	2–14	62	55%	55%		
Griffiths & Scholtmeijer 1987 [9]	2–15	104		**25% (23%)	**14% (25%)	
Scholtmeijer & Nijman 1994 [19]	0.1–15	101	38%	38%		
Koff et al. 1998 [20]	after bladder control	143	46%	27%	23%	46%
Yeung et al., 2006 [21]	1–11	82	55%	*38	*27	

*% of those with bladder dysfunction, **in brackets additional number with OAB and dysfunctional voiding, respectively, but with some uncertainty of the diagnosis.

In studies of larger cohorts of children with VUR, the prevalence of all bladder dysfunction together was reported to be between 18% and 50%, using questionnaires and flow measurements for the diagnose [12, 14, 16]. In one of the studies, the international reflux study in children [12], differentiation of the dysfunction entities was done and they were found to be almost equally common (Table 1). This latter relation was also seen in urodynamic investigations [9, 20, 21], although the total number of children with dysfunction was higher in those studies (Table 1). This relation between OAB and dysfunctional voiding is very different from what is considered to be the case in cohorts of children with voiding dysfunction without VUR, in which OAB is much more common than dysfunctional voiding, especially in nonurodynamic studies [24] but even in urodynamic studies [25].

The concept dysfunctional elimination syndrome (DES) was introduced by Koff et al. in 1998 [20], including infrequent voiding, constipation, and often symptoms of an overactive detrusor. He reported it to be present in 46% of children with primary reflux (Table 1). He found that both the rate of UTI and spontaneous resolution of VUR were adversely influenced by the presence of dysfunctional elimination syndrome. He also noted that in the children who had detrusor overactivity as their main dysfunction, the likelihood of recurrent UTI was lowest, indicating that the OAB dysfunction was less severe.

These latter results were in line with what was seen in a followup study at the age of 7 years of 20 children who presented during infancy with grade 4-5 VUR and bladder dysfunction, diagnosed at that time. The dysfunction was characterised by high bladder capacity and incomplete emptying. At the followup, these children had infrequent voiding, and often did not void at school or in the morning if not prompted by parent or other guardian. Constipation had been or was still a problem in the majority of these children [26]. The reported bladder and bowel dysfunction in these children with congenital reflux was very similar to the DES children as reported by Koff et al. [20]. In these cases, DES actually seems to be a part of the VUR complex and present already from infancy, and might even be suggested to be a congenital problem, rather than an acquired one.

However, in other studies it has not been possible to diagnose dysfunctional elimination syndrome more often in children with VUR than in control groups. Shaikh et al. [27] investigated the prevalence of DES at school age, in a cohort of children with a history of UTI before the age of 2 years. They had a control group of similar age but without a history of UTI. DES was diagnosed in 20% of the children in both groups. In the UTI group, the prevalence of DES did not differ in children with and without VUR, identified earlier in life. The authors conclude that neither UTI nor VUR diagnosed in early childhood was associated with an increased likelihood of DES later in life. Similar results were found in multivariate analyses of a large pediatric patient database with the aim of describing the relationship between DES, sex, VUR, and UTI [28]. Of the total number of patients (2759), about two-thirds had VUR. DES was seen in 35% overall, with the highest prevalence in patients without VUR but with a history of UTI (52%). The lowest frequency was found in VUR without UTI (22%), whereas in those with VUR and UTI it was 39%. Thus DES was less common in VUR children than in children without VUR, especially if not found together with UTI. Another important finding was that girls had a significantly higher rate of DES than boys.

Prevalence of VUR in children with bladder dysfunction

In studies where the inclusion criterion was idiopathic bladder dysfunction, the prevalence of VUR was between 14% and 47% [25, 29, 30] (Table 2). The variation was probably attributable to selection of patients referred to the

unit. The lowest frequency was found in a urodynamic study of 1000 consecutive children referred to a large urotherapy unit. In this latter study, less selection of patients can be suggested than in the other studies cited, since in these other studies the patients were referred to a pediatric urological clinic.

4. TREATMENT OF VOIDING LUT DYSFUNCTION AND ITS EFFECTS ON VUR IN CHILDREN WITH BLADDER CONTROL

The registration of severity of voiding LUT dysfunction and its response to treatment with regard to symptoms is often highly subjective, since the definition of how often the symptoms are experienced is seldom given. Furthermore, in most cases a number of symptoms are included. Using a symptom score has been suggested in order to overcome this obstacle. Upadhyay and coworkers [31] reported on a group of children with both bladder dysfunction and VUR using symptom score to evaluate severity of bladder dysfunction before any treatment and also to record the results after treatment at followup. Overall after 2 years, resolution and downgrading of VUR was 58%, with a decrease in symptom score from 9.6 to 3.7 in this group. In the group without improvement of the reflux, on the other hand, the symptom score went from 14.4 to 11.1, that is, a higher initial score and also poor response to the treatment. The weakness of the scoring system is that all symptoms have the same value, no symptom is considered more serious than another.

Overactive bladder

The results of treatment of overactivity in relation to VUR resolution are conflicting. Most studies do not have a control group, include only a small number of patients, are retrospective, and have nonuniform ways of diagnosing overactivity, which might explain the different results. Many studies suggest increased spontaneous resolution after such treatment [18, 32, 33] (Table 3). As early as 1983, Koff and Murtagh [18] reported that anticholinergic treatment of detrusor overactivity in 26 girls gave a VUR resolution rate of 44% during a 4 year followup, as compared with a group of children with VUR but without detrusor overactivity, in which the resolution was only 17%. In a similar comparison, Scholtmeijer and Nijman [19] found only a slightly higher rate of improved grade of VUR in the group treated for detrusor overactivity (Table 3).

Conversely, Willemsen and Nijman [34] showed, in a prospective study of 102 children, that treatment of the group with detrusor overactivity (41 children, 40%) with anticholinergic drugs did not increase their resolution rate, as compared with a group without overactivity. The overall resolution rates were 51% and 55%, respectively for those with and without overactivity (Table 3). An increased rate of UTI, however, was found in the children with bladder overactivity.

Whether spontaneous resolution of VUR in a group with untreated OAB is different from a group without OAB cannot be established from the studies available.

Dysfunctional voiding (DV)

There are very few studies reporting on VUR and treatment of isolated DV, while there are more on DV and detrusor overactivity seen together.

Kibar et al. [36] reported on treatment with biofeedback in children with DV and VUR. The overall resolution rate after less than one year of followup was 63% (Table 3). No controls were used. Similar results was reported by Palmer et al. [35], with resolution in 55% and downgrading in 16% of VUR one year after biofeedback treatment of DV (Table 3). Grades of VUR were mainly I-III in the latter study, while in the former some grade IV were also included.

Homsy et al. [32] reported as early as 1985 that treatment of bladder dysfunction (overactivity only or together with dysfunctional voiding) with anticholinergics influenced the spontaneous resolution rate of VUR. He noted that a small subgroup of children without incontinence had a VUR resolution of only 6%, whereas in those with urinary incontinence the resolution rate was 68% during 2.5 years of treatment and followup.

Snodgrass [15] noted a lower resolution rate of VUR in children with dysfunction. The problem with the presentation of this cohort of children with VUR and bladder dysfunction was that OAB and dysfunctional voiding were not differentiated. This is a problem when it comes to treatment with oxybutynine. This treatment may be contraindicated in dysfunctional voiding because of incomplete emptying before start of treatment, thus inducing higher risk for UTI, which was seen in his series.

However, including studies in which bladder dysfunction was characterised by a dysfunctional voiding pattern, data support the assumption that there is a decreased spontaneous resolution of VUR in children with this dysfunction, especially when seen in combination with high-grade VUR.

Yeung et al. [21] showed, in children between ages one and eleven, that bladder dysfunction and renal abnormalities were significant negative prognostic factors for resolution. He did not report on any treatment or its possible treatment effects on this rate. The same finding was established in the IRSC study [12], that is, children with bladder dysfunction had a lower resolution rate of reflux.

DES in children with VUR was also correlated to a lower resolution rate [20], despite treatment of both the bladder and bowel dysfunction. Similar results have been reported in studies before the age for bladder control. In these studies, the dysfunction was characterised by high capacity bladder and incomplete voiding [6, 10]. In a study where this kind of dysfunction was diagnosed before the age for bladder control, treatment with clean intermittent catheterisation did not increase the spontaneous resolution rate in 20 children with grade 4-5 VUR [37].

5. BLADDER DYSFUNCTION AND RESULTS OF SURGICAL/ENDOSCOPIC VUR TREATMENT

It has previously been suggested that reimplantation of the ureter into the bladder in a child with major voiding dysfunction carries a high risk of failure. The dysfunction

Table 2: Prevalence of VUR in patients with bladder dysfunction. Urodynamic studies.

Reference	Age (years)	Patients with bladder dysfunction (number)	Overactive bladder (% of patients with VUR)	Dysfunctional voiding (% of patients with VUR)	Patients with VUR (% of total)
*Koff et al. 1979 [30]	2.5–17	53	100%		47%
Hoebeke et al. 2001 [25]	9–10	1000	58%	31%	14%
Ural et al. 2008 [29]	1.5–15	340	71%	6%	46%

*Only patients with UTI included.

Table 3: Impact of treatment of bladder dysfunction on spontaneous resolution of VUR.

Reference	Age (y)	Patients (number)	VUR grade	Bladder dysfunction	Treatment	Follow/up (y)	Resolution (downgrading)	Controls resolution (downgrading)
Koff & Murtagh 1983 [18]	2–14	62	I-IV	OAB	Anticholonergics	4	44% (16%)	17% (0%)
Scholtmeijer & Griffiths 1990 [33]		25	I-IV	OAB	Anticholinergics	1	37% (22%)	No controls
Scholtmeijer & Nijman 1994 [19]	0.1–15	39	I-IV	OAB	Anti-cholinergics	3	38% (38%)	40% (16%)
Willemsen & Nijman 2000 [34]	0.1–15	102	I-V	OAB	Anti-cholinergics	5	51%	55%
Palmer et al. 2002 [35]	6–10	25	I-III	DV	Biofeedback	1	55% (16%)	No controls
Kibar et al. 2007 [36]	7.2	78	I-IV	DV	Biofeedback	0.5	63% (29%)	No controls
Homsy 1985 [32]	4–11	35	I-IV	OAB + DV	Oxybutynine	2.5	50% (22%)	No controls
Snodgrass 1998 [15]	3–10	128		OAB + DV	Oxybutynine		45%	61%

that carries the high risk is a severe form of dysfunctional voiding, induced by functional obstruction during voiding [22, 38]. Regarding endoscopic VUR treatment, milder forms of voiding LUT dysfunction did not influence the results of endoscopic injection treatment for VUR in a recent study [13], in which the dysfunction disappeared after cessation of the reflux. The authors suggest that the reflux was an underlying cause of the dysfunction in these cases. Additionally, they observed that a high proportion of those requiring a second injection had persistent bladder dysfunction of a different kind, characterised by high bladder capacity and infrequent voiding. This again suggests that the dysfunctional bladder, but not the isolated OAB, is a risk for failure of active reflux treatment. Another study reported that the success rate was lower after a second injection in children with bladder dysfunction [39]. In this study, the type of dysfunction was not specified.

6. UTI, BLADDER DYSFUNCTION, AND VUR

Recurrent UTIs have been shown in many studies to be higher in VUR patients with bladder dysfunction than in VUR children without such dysfunction [6, 15, 20]. This was most obvious in children with emptying problems such as in DV and DES as well as in children with congenital high-grade reflux and incomplete emptying.

Snodgrass [15] showed a higher frequency of UTI in children with VUR who also had bladder dysfunction. The dysfunction was treated with oxybutynine in all cases. The problem with the presentation of this cohort of children with VUR and LUT dysfunction was that OAB and dysfunctional voiding were not differentiated. This is a problem when it comes to the treatment with oxybutynine, since it may be contraindicated in dysfunctional voiding because of incomplete emptying before starting treatment, thus inducing higher risk for UTI.

7. RENAL SCARRING, BLADDER DYSFUNCTION, AND VUR

Most of the studies reporting on children with VUR and the OAB dysfunction have not found any difference in numbers of children with renal damage in the groups with and without the dysfunction [17, 18]. In a study including a small number of patients, however, a slightly higher number of damaged kidneys were seen in children with VUR and OAB [40]. On the other hand, differences between those with DV and the OAB dysfunction have been identified, with higher frequency of renal damage in children with DV [9].

8. CAUSAL CONNECTION BETWEEN VUR AND BLADDER DYSFUNCTION

The bladder function pattern with high capacity bladders and incomplete emptying seen at follow up in children presenting during the infant year with high-grade VUR [6, 10] is similar to the dysfunctional voiding pattern seen in older children [9, 12]. The majority of children with congenital high-grade VUR have been reported to have recurrent UTI and renal damage, as well as poor spontaneous

resolution of the reflux [6, 10], which is also similar to what has been reported for older children with VUR and dysfunctional voiding [9, 12, 15]. The dysfunctional voiding can be suggested to be a milder form of the Hinman bladder [22]. In the Hinman bladder, the dysfunction is thought to be the primary problem and acquired after age for bladder control, and the cause of VUR. In the congenital high-grade VUR, on the other hand, both the dysfunction and the VUR may be congenital. Actually, a common cause of the reflux, the bladder dysfunction and the general hypo/dysplasia often seen in the ipsilateral kidney, can be suggested. An anomaly in the ureteric bud region could be suggested to induce the VUR and the renal anomaly. Since these embryological structures also form the bladder outlet, the dysfunction of the bladder might theoretically also have the same origin [41]. A more severe form of congenital dyscoordination, than the physiological, is another possibility.

The extra volume load induced by the refluxing urine volumes, which circulate between the bladder and the upper urinary tract, might also be a factor of importance for the high capacity bladder. In such cases, the bladder problems should more or less disappear after surgical treatment of the reflux. Investigation of bladder function in a group of children ages 7-8 years who had been surgically treated for high-grade reflux at the age of median 4 years did not support this theory. These children were diagnosed early as having a bladder dysfunction characterised by high-capacity bladders with incomplete emptying. At the follow-up investigation, they still had high capacity bladders with few voiding per day but their emptying ability had improved, with quite low volumes of residual urine [26]. The results of this study did not support the theory of the refluxing volumes as a cause of the high capacity bladder.

The connection between the overactive bladder dysfunction pattern and reflux is less clear. It is difficult to consider bladder overactivity the cause of reflux, since it causes only intermittent increases in bladder pressure, which is not thought to induce reflux if the junction is competent. Only a concomitant obstruction inducing a continuous pressure problem in the bladder is considered to be able to induce VUR in parallel to what is seen in children with the NBD or anatomical urethral obstruction, for example, in boys with PUV. The other possibility is that there is only marginal competence in the valve mechanism, and in these cases the detrusor contractions against a contracted sphincter may induce VUR. If this latter causality exists, it might explain why renal damage seldom is seen in children with an OAB [9]: the pressure influencing the kidneys is only intermittent. Furthermore, these children are often recognised after toilet training age, that is, VUR is not congenital but occurs when the kidneys can be suggested to be less vulnerable. In addition, VUR is often of low grade. A few studies have shown a similar number of patients with renal abnormalities both in groups with bladder overactivity and in groups with stable bladder [17, 18]. In these studies, the control group was, however, children with VUR but without any bladder dysfunction.

9. COMMENTS

VUR is associated with both OAB and dysfunctional voiding, with different entities as described above. However, we can only speculate about the precise causative mechanisms between the respective dysfunction and VUR. There are divergent opinions concerning whether the treatment of the overactive bladder influences the rate of spontaneous resolution. There are as yet no randomised studies investigating the effect on the reflux of treatment of the OAB versus no treatment. To my knowledge, there are no studies comparing a group of children with VUR and untreated OAB with a group of children with VUR and a stable bladder.

In children with dysfunctional voiding and VUR, it is easier to see a causative connection, especially in the more severe forms of VUR, since this can be considered parallel to neurogenic bladder dysfunction. It is not known whether this is an acquired dysfunction as most authors suggest or if it is a congenital anomaly and part of a complex that also includes VUR.

Treatment of the dysfunctional voiding increases the spontaneous resolution rate as has been suggested in some studies, but not in others. Since there are no randomised studies available comparing resolution rates in treated children with untreated children, this cannot be established. However, what is known is that dysfunctional voiding, dysfunction elimination syndrome, and the similar dysfunction seen in children with high-grade congenital reflux, all have negative influences on the spontaneous resolution rate of VUR when untreated, and lead to an increased risk for recurrent UTI.

Since there seems to be a lower resolution rate in children with dysfunctional voiding than in those with OAB, it is important to distinguish between the diagnoses when comparing VUR resolution rates of children with and without dysfunction. OAB in its genuine form seems to be a much more benign dysfunction than dysfunctions including incomplete emptying of the bladder. However, it should be remembered that bladder overactivity and dysfunctional voiding are often seen together.

In summary, the question if treatment of bladder dysfunction improves prognosis for spontaneous resolution of reflux cannot be answered from the studies available. This is true for the overactive bladder, the dysfunctional voiding, as well as the dysfunctional elimination syndrome. Randomised studies have to be performed to give an answer. In these studies also the definitions from the ICCS standardisation document have to be used, to avoid confusion about terminology. Maybe the use of a scoring system of bladder dysfunction symptoms would be useful as well. However, treatment of bladder dysfunction should of course be recommended, especially in cases with dysfunctional voiding and DES. One reason is that the success of surgical treatment of the reflux, both endoscopic and open, probably depends on the bladder function status. The most obvious reason for treating the bladder dysfunction in these refluxing children is, of course, as in nonrefluxing children, the symptoms of urgency, urinary incontinence, constipation, UTI, and so on.

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Review Article

Interactions of Constipation, Dysfunctional Elimination Syndrome, and Vesicoureteral Reflux

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Vesicoureteral reflux (VUR) is simply described as incompetence of the unidirectional valve at the ureterovesical junction (UVJ), leading to backflow of urine to the kidney. Today, it is clear that VUR is not only related to the UVJ function but also to a combination of processes including immunity, bladder and pelvic floor function, dysfunctional voiding, and constipation. Although our surgical aims directed towards improving the valve coaptation at the UVJ, we understand today the importance of the diagnosis and treatment of constipation and dysfunctional voiding adjunctively.

1. INTRODUCTION

The frequency of stools in most children decreases from a mean of four per day in the first week of life to 1.7 per day by the age of 2. Over this interval, stool volume increases more than tenfold, while maintaining a consistent water content of approximately 75%, and the intestinal transit time from mouth to rectum increases from 8 hours in the first month of life to 16 hours by the age of 2 to 26 hours by the age of 10 [1, 2].

Constipation generally is defined by the hard nature of the stool, the pain associated with its passage or the failure to pass three stools per week [1]. In most children, functional fecal retention is the most common chronic disorder of defecation caused by the voluntary withholding of feces due to fear of painful defecation. Many events may lead to unpleasant defecation such as aggressive toilet training; for instance, as children approach toilet-training age, the child's gratifying impulse to defecate is in conflict with parental constraints to establish bowel control and a premature or excessive parental emphasis on continence may lead the child to the decision to withhold the stools [3]. Other causes for fecal holding are changes in routine or diet, an intercurrent illness, or postponing the defecation because the child is too busy or toilets are unavailable [3, 4]. Once the child has experienced the painful passage of hard stool, he or she attempts to avoid the expected discomfort by exerting voluntary withholding. The rectum accommodates to the contents and the urge to defecate gradually vanishes. As the cycle is repeated, greater amounts of hard stool are built up in the rectum and pass with even greater pain, frightening the child [5, 6].

It has been reported that 34% of toddlers in the UK and 37% of Brazilian children younger than 12 years were considered by their parents to be constipated [7]. In the absence of painful symptoms, parents are generally unaware of the bowel habits of children older than 4 or 5 years. It is our experience that parents paid little attention to the frequency of their child's bowel movements, but paid much attention to the number of urinary and fecal incontinence episodes.

Encopresis or fecal soiling is usually the result of looser stool leaking or overflowing from a rectum that has been distended by retained stool; soiling occurs whenever the child tries to expel gas or the muscles which are used to withhold become fatigued. While encopresis is three to six times more common among males than females [1], we observed that voiding position may contribute to this higher prevalence of soiling in boys, as they stand to void, thus soiling in their

underwear unknowingly. We speculate that the difference in females is that they remove their underwear and will sit on the toilet to void. Thus, the natural voiding position has a direct impact on the statistics of encopresis in boys compared to girls.

2. IMPACT OF CONSTIPATION ON THE URINARY SYSTEM

There are many reports correlating constipation with functional bladder-outlet dis-coordination being responsible for urinary incontinence, urinary tract infections, vesicoureteral reflux, and even false uroradiologic pathology [8–11]. The impacted stool in the rectum compresses the bladder, reduces its functional capacity, and provokes earlier sensation to void. In addition, chronic pelvic floor spasm prevents complete relaxation during voiding, and will attribute to postvoid residuals. Klijn et al. [12] showed that the diameter of the rectum in patients with dysfunctional voiding is higher compared to asymptomatic healthy children. The average rectal diameter in the dysfunctional voiding and constipated patients was 4.9 cm versus 2.1 in the control group ($P < .001$)

Kasirga et al. [13] compared 38 children concerning chronic functional constipation to 31 healthy children and found significant higher frequency of urinary tract infection and urgency. Neumann et al. [14] found that 34% of children with urinary tract infections had abnormal bowel patterns, and most parents were not forthcoming with this information. O'Regan et al. [11, 15] noted that constipation was associated with recurrent urinary tract infections and bladder instability in girls. They found that 50% of the mothers denied constipation to be present in their children, but questioning of the individual children revealed that most had only 2 to 3 bowel movements per week. O'Regan et al. [11, 15] also showed that children with enuresis had constipation. In 22 children with enuresis, rectal examination and rectal manometric studies proved constipation. Treatment of constipation resulted in resolution of enuresis. Uninhibited bladder contractions, observed in enuretic constipated children, were also noted in children with constipation alone, suggesting that constipation is a commonly unrecognized etiologic factor in enuresis [16].

Loening-Baucke [7] evaluated the frequency of urinary incontinence and urinary tract infection in 234 chronically constipated and encopretic children before, and after the start of treatment for constipation. Followup, at least 12 months after commencement of treatment, revealed that the constipation was relieved successfully in 52% of the patients. Relief of constipation resulted in disappearance of daytime urinary incontinence in 89% of the patients, nighttime urinary incontinence in 63% of the patients, and disappearance of recurrent urinary tract infections in all patients who had no anatomic urinary abnormalities.

3. CONSTIPATION DYSFUNCTIONAL ELIMINATION SYNDROME AND REFLUX

Numerous studies connected between vesicoureteral reflux and dysfunctional elimination syndrome (DES). O'regan et al. [17] correlated the directly established association of reflux, uninhibited bladder conduction, and constipation. The author examined urodynamic and rectal manometry on 17 children with VUR. All 17 had rectal dilatation and uninhibited bladder contraction confirming the vicious connection of these 3 conditions.

Koff et al. [10] assessed the influence of functional bladder and bowel disorder on the natural history of children with primary reflux. The authors assessed 143 children who had either spontaneous resolution of VUR or (82%) had breakthrough infection that led to definitive surgical management. Among patients without DES, only 18% had breakthrough infections and surgical correction. The rate of DES was higher in children with breakthrough infections, 77% versus 23%. The spontaneous resolution of reflux was longer in an average of 1.6 years in children with DES. Moreover, unsuccessful surgery or development of de novo contralateral reflux and post-successful surgery urinary tract infections appeared only in patients with DES. Care should be taken in the interpretations of the results of this paper as patients were selected to this study based on the presence of reflux. Naseer and steinhardt [18] demonstrated deleterious effect of dysfunctional voiding on VUR treatment end point—the development of scars. Among 538 with DES, 192 (13.5%) already had scars at initial assessment, 31 (2.1%) developed new scars despite meticulous care by the urology clinic. Eleven of those were referred to surgical treatment, however 6 developed new scars despite successful surgery.

Silva et al. [19] tried to identify independent factors predicting the resolution of VUR. DES was one of the 4 independent predictors for VUR resolution. The author concluded that treatment of DES is a cornerstone in the management of VUR. Upadhyay et al. [20] too demonstrated the relationship between DES, DES management, and the resolution of VUR. Using a DES standardized symptom score which included questions regarding bladder and bowel habits, the authors showed direct correlation between improvement in the symptoms score and resolution of VUR. In 7 patients with spontaneous resolution of VUR, there was also statistically significant symptom score improvement, in addition 4 patients showing the same symptom score improvement had also reduction of at least 2 grades in VUR grading. Improvement monitored by symptom score showed compliance to behavioral therapy and could predict VUR improvement and resolution.

In contrast to the above-mentioned studies, Sheikh et al. [21] assessed the relationship between early UTI, DES, and VUR. The authors examined 248 children, 123 of them had culture-proven UTI diagnosed by the age of 2. Control group consisted of 125 patients to whom urinalysis was performed due to fever ruled out UTI. Questionnaire given to all children showed no significant presence of DES (22% versus 21%). In patients with UTI who were later diagnosed with VUR, DES was present in 18% compared to 25% of those without VUR. The authors concluded that neither UTI nor VUR diagnosed before the age of 2 was associated with DES in school-aged children. The rate of DES is lower in patients with UTI and VUR compared to those without VUR, however there is still a significant percentage of

patients with UTI and VUR who had DES. Chen et al. [22] studied 2759 patients who had renal sonography and voiding cystogram for various clinical entities. The authors used multivariate logistic regression approach to quantify the associations between DES and other pediatric urology factors. They showed that DES is present in 36%-36.1% of girls with unilateral and bilateral VUR, and in 20.5–21.2% of boys, respectively. The higher rate of DES in girls was independent of UTI and VUR status. In patients that diagnosed with VUR due to other entities beside UTI (sibling VUR, prenatal hydronephrosis, etc.), the association to DES was negative. Although this evidence may oppose the hypothesis that relationship between DES and VUR exists, however we think that these results clearly reflects the variety of patients categorized under VUR. Indeed, sibling VUR and VUR detected for other reasons rather than UTI is usually considered less significant, and the lower rate of related DES and UTI may give the explanation why. In this study, patients with VUR and UTI had almost doubled risk of DES supporting our belief that DES plays a major role in the pathophysiology of VUR.

4. CONCLUSIONS

Constipation plays a major role in the function and dysfunction of the urinary tract. Patients with constipation have concomitant urinary tract problems including infection, incontinence, enuresis, and VUR. There are strict evidences that constipation is related to the presence of reflux, urinary tract infections, breakthrough infections, presence of scars, and the appearance of new scars. Patients with constipation and DES have lower and longer rates of spontaneous resolution of reflux and vice versa, adherent to behavioral treatment, and improvement of the constipation is related to spontaneous VUR resolution.

Evaluation and treatment of constipation and DES should be an integral part of the initial assessment and management of a child with VUR, it would be also advocated to postpone definite surgical correction in patients with severe DES in order to improve surgical outcome.

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Case Report

Vesicoureteral Reflux in the Child with Lazy Bladder Syndrome: The Infrequent Voider

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Recommended by Hiep Nguyen

The Infrequent Voider Syndrome or Lazy Bladder Syndrome in children is characterized by a large capacity bladder, frequently associated with a significant volume of residual urine. Usually these patients arrive at medical examination with a history of recurrent urinary infections but without anomalies in the upper urinary tract. We report about a young girl affected by one-sided 2° degree vesico-ureteral reflux due to Lazy Bladder Syndrome that had never been diagnosed before. This patient has been submitted to a prompt bladder training and seems presently to have at last gained a physiological micturition after 9 months of follow-up, without actual evidence of vesicoureteral reflux. Therefore we must stress that it is prominently important considering about infrequent micturition in a paediatric case history or a large capacity bladder, possible presence of bladder dysfunction and vesicoureteral reflux too.

1. INTRODUCTION

It has been known for nearly 30 years that there are children (mainly girls) who acquire abnormal micturition patterns in their first years of life, even without neurological or urological injuries. Such anomalies may lead to a sheer bladder disorder. Every child that is affected by altered bladder dynamics is at risk of developing pathologies such as urinary infection, vesicoureteral reflux (VUR) and so on.

We report about "a classic" case of Infrequent Voider Syndrome that we observed after the patient wandered for a long time across several other urologic and paediatric services. This is an evidence about how such a clinical picture has not an easy diagnosis and is often ignored.

2. CASE REPORT

About 2 years ago a 5-year-old girl with recurrent urinary infection was admitted in another hospital and checked. A 2° grade active right vesicoureteral reflux was found by voiding cystourethrography. She was treated by assuming orally a long-term antibacterial therapy: a prophylactic evening dose of trimethoprim-sulfa combination. After one year vesicoureteral reflux remained unchanged by X-ray check and she had a urinary infection relapse for a temporary break in antibacterial therapy. The parents took her to another urological department and were advised to submit their daughter to ureteral reimplantation surgery.

They were not persuaded and took their little girl to our outpatients' department.

She was a little girl presenting normal somatic characteristic for her age, quite shy and affectively deeply attached and dependent from her mother who accompanied her. Her physical objectivity did not signal anything which could lead to urological pathologies. Looking at the cystourethrography (Figure 1) we observed a large vesical capacity, abnormal for the patient's age; an ultrasound exam of the urinary tract confirmed this observation: her bladder contained a volume of 500 cc.

The girl seemed calm with no need of urinating. Finally, persuaded by her mother she had an uroflowmetry test; the girl completely emptied her bladder, urinated 500 mL, with a normal flow.

Searching in the remote pathological anamnesis we found that the girl had always urinated rarely, twice or three times a day, remaining sometimes for more than 12 hours without urinating.

She had often refused to urinate in the evening before going to sleep, saying she did not need to.

Her mother did not attribute any importance to this habit and she did not insist. In both of them it was clear a fear of urinating in bathrooms out of their home because of the scarce hygiene conditions and the past urinary infections of the girl.

The patient refused every kind of invasive diagnostic approach such as urodynamic examination, cystoscopy. We could proceed in the diagnosis only by asking a micturition diary which has confirmed our clinical suspect of Lazy Bladder Syndrome.

From a therapeutic point of view, the girl has been directed to a bladder training therapy.

We only used behavioral therapy notifying to the girl a strict daily micturition scheme to modify the child's voiding habit and achieve a different behavior which included more frequent micturition and a new conception of the use of public toilettes. Consulting did not prescribe any other approach considering the good level of cooperation of the girl.

The absence of evident postmicturition residuals enabled us to avoid anticolinergic-alpha-adrenergic blockade therapies or invasive procedures such as intermittent catheterization or endovesical electrical stimulation.

After 9-month follow-up the patient seems to have changed her micturition habits; she is still following a prophylactic antibacterical therapy.

The last ultrasonographic evaluation does not show any negative evidence of the upper urinary tract.

The cystography check done 9 months later than the previous one and after 6 months of behavioral therapy pointed out the disappearance of the vesicouretheral reflux.

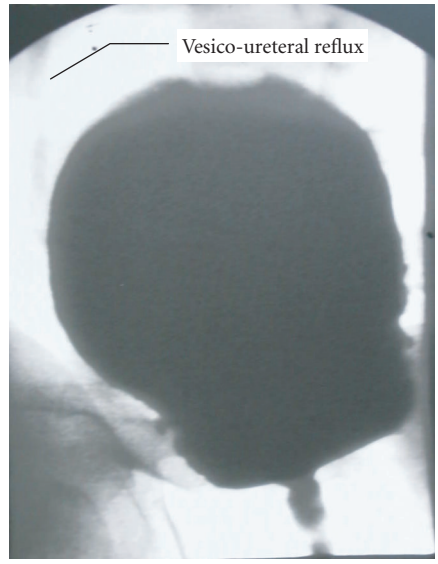


Figure 1: Large vesical capacity and vesicoureteral reflux at cystourethrography.

3. DISCUSSION

The Lazy Bladder Syndrome mostly concerns young girls. The history usually starts at 5–10 years of age with urinary infections, daytime incontinence, or as an accidental report during a consulting for other purposes.

Typically the bladder is expanse, easily palpable as it can have a urine content of more than 1 litre, often with a conspicuous postmicturition residual and surprisingly a normal upper urinary system.

The cause is unknown, but it probably has a behavioral origin. It regards children who learned to retain the urine for long periods. It is not uncommon that their parents inculcated them, even if not intentionally, the fear of contaminate themselves or even the idea that it is "evil" getting wet of urine.

It is often found in children excessively tidy or clean which makes them avoid any toilette that is not their own one.

They often urinate only in the morning and in the evening to avoid the school bathrooms.

There are some other children who had in their first years painful micturition because of urinary infections, and they still have a deep fear of it, getting used to urinate as less as possible [1].

Next to these clear clinical cases, we can find less evident ones in which we can find the absence of postmicturition residual but always high capacity bladders, as in our case report.

The uroflowmetry test can appear morphologically normal, making it harder to recognize a latent bladder disfunction, which can lead, if not treated, to irreparable damages of the upper urinary tract (Hoebeke et al. found in these children 17% VUR and Njman 20%) [2, 3]. Therefore, the risk run by our little 4-year-old patient was very high.

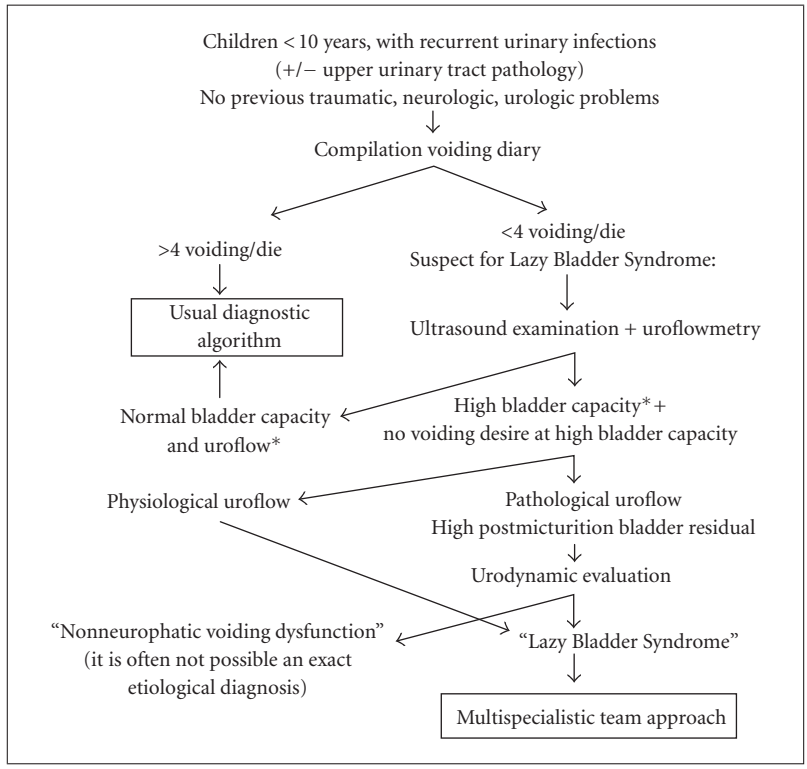
An urodynamic evaluation may prove, in advanced cases, detrusor hypocontractility from the permanent bladder iperextension and the need of a quite strong abdominal effort, depending on the coexistence of vesical sphincter dyssynergy, therefore a high pressure bladder emptying.

It is possible that in some cases, this determines and prevents the spontaneous resolution of a ureteral reflux, as in our case report, considering the correlation between reflux, capacity, and bladder pressure.

In these cases, the rieducative treatment of bladder training becomes necessary to lead the child to urinate psychologically without effort, without bladder iperextension trying to recover the vesicoureteral junction competence and a normal bladder volume. In fact, it is very difficult to gain some advantages when voiding disorders have already caused important alteration of urinary apparate. It is arduous to differentiate between lazy bladder and neurological bladder syndrome.

This is why an early diagnosis can be more advantageous than ever and we believe that the finding of a high bladder capacity in the child with infrequent micturition has to be always considered with worry and accurately evaluated, as a possible clinical expression of Lazy Bladder Syndrome.

To sum up, always for the purpose of an early diagnosis, we propose a diagnostic algorithm (Algorithm 1).



Algorithm 1: Diagnostic algorithm for Lazy Bladder Syndrome (*Bladder Capacity = age (years) + 2 × 30 mL).

The management of vesicoureteral reflux (VUR) should be performed after a careful diagnostic approach. It is important to remember that high-bladder pressures may induce VUR. Voiding frequency, bladder capacity, and residual urine volume are key points facing children with recurrent urinary tract infections (UTIs).

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Review Article

Diagnostic Approach to Reflux in 2007

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Recommended by Walid A. Farhat

There is ongoing controversy regarding the association between vesicoureteric reflux (VUR), recurrent urinary tract infections (UTI), and renal damage. Despite this, routine work up for VUR is still recommended after febrile UTI in most children. The present article reviews the indications and imaging modalities available for VUR diagnosis. Alternative newer techniques like MR cystography and voiding urosonography are discussed. The increasing evidence of the role of DMSA scans in managing children with VUR is highlighted.

1. INTRODUCTION

The goals of an imaging procedure in general are to confirm the diagnosis suspected with a high degree of sensitivity and specificity, to aid treatment and allow prognostication. On the other hand, it is obligatory for the treating physician to analyze the risks and benefits of the diagnostic procedure and understand the natural history of the disease in question to establish whether or not the diagnosis and treatment of a condition would alter long term outcome or impact management decisions.

The diagnosis of vesicoureteric reflux (VUR) is a relatively straightforward and well-established procedure. However, the underlying rationale for identifying VUR to prevent recurrent pyelonephritis (PN) and long-term renal damage has been vigorously questioned in the recent literature [1–4]. Coupled with this, there has been the increasing awareness of the risks of radiation exposure and the realization that VUR investigation is an invasive procedure and definitely an unpleasant experience. Therefore, it is imperative for the pediatric urologist and nephrologist to reevaluate the indications and goals for imaging for VUR, redefine the modalities used, and establish guidelines for followup.

The current article reviews the available modalities for evaluating VUR, suggests protocols for investigating children with suspected VUR, and presents the recent evidence justifying these recommendations.

2. IMAGING MODALITIES FOR DIAGNOSIS OF VUR

2.1. Voiding cystourethrogram (VCUG) or radionuclide cystogram (RNC)

An ideal test for VUR detection would be one involving no radiation, no bladder catheterization, no sedation, low cost, high sensitivity, and one which provides complete anatomical details. The traditional method for diagnosing VUR is the fluoroscopic voiding cystourethrogram (VCUG). Currently, radionuclide cystography (RNC) remains the primary alternative to a VCUG in evaluating VUR. The objection to performing a VCUG is related to the high radiation exposure of a traditional VCUG which is believed to be about 100 times that of a RNC. However, with the judicious use of digital and pulsed fluoroscopy with meticulous image coning, the radiation exposure from a VCUG has been significantly reduced [5]. Despite these measures, the average ovarian radiation dose was shown to be about 10 times greater in a VCUG when compared with an RNC [6]. The proponents of RNC argue that this effectively reduces the sensitivity of the VCUG in identifying VUR as snapshots of the bladder filling and voiding are taken rather than continuous imaging. In an editorial comment, Benson stated that "the radiation dose given during 3 minutes of fluoroscopy time approximates that of two pelvic spiral CT scans with contrast, 1.5 conventional abdominal CT

scans without contrast, 3 DMSA scans, 60 abdominal plain films, 600 radionuclide VCUG's, or 10 years of background radiation" [7].

Several studies have compared the sensitivity of VCUG and RNC and concluded that RNC is at least as sensitive as or more than a VCUG for detecting VUR [8–10]. Sükan et al. observed no significant difference between the 2 modalities but noted that RNC offered a higher sensitivity in the younger age group [8]. Moreover, despite not reaching statistical significance, in children with a positive dimercaptosuccinic acid (DMSA) scan, RNC identified VUR in a higher percentage of children as opposed to the VCUG. This is a relevant finding in the current era where a positive DMSA scan is believed to be an important finding in children presenting with PN (as discussed later). An insignificant grade 1 VUR may be missed on an RNC but the continuous imaging during filling and voiding allows greater detection of VUR, which is an intermittent phenomenon. For both tests, it is well established that a cyclic study should be performed to increase the detection of VUR [11]. The definite advantage a VCUG has over an RNC lies in the anatomical information obtained by the former especially in evaluating the urethra in males. Moreover, the International Reflux grading system is based on the VCUG and since most studies on VUR have used this grading system, treating physicians feel more comfortable in knowing this information. However, again as a result of change in treatment philosophy, it can be argued that a broader classification of VUR into dilating (≥Grade 3) and nondilating varieties is possible on an RNC, making this an insignificant issue when deciding on the study to obtain. Therefore, currently VCUG remains the standard when initially evaluating a child with suspected VUR. For all subsequent studies, the RNC is the preferred modality. Medina et al. performed a cost analysis of VUR imaging using VCUG and RNC, highlighting another potential reason for preferring the RNC for followup imaging [12]. The study showed that the direct costs of performing a VCUG was 1.74 times higher than an RNC ($P < .001$).

2.2. Indirect RNC

The indirect RNC offers the possibility of detecting VUR without bladder catheterization and presumably in a more physiological setting with natural bladder filling. The additional advantage is the ability to assess upper tract differential function and drainage with the injected radioisotope. Although a few reports have shown a comparable degree of sensitivity between the direct and indirect RNC, the consensus is that due to an inability to study the filling phase with an indirect RNC there is a considerable false negative rate with indirect RNC [13–15]. There may be a role of the indirect RNC as a followup study in children who are toilet trained [14].

2.3. Voiding urosonography (VUS)

The sonographic evaluation of VUR following intravesical instillation of US contrast agent has gradually popularized VUS over the last decade. In a comprehensive review of VUS when compared with VCUG, Darge showed that in 1338 patients with 2893 refluxing units, VUS showed a diagnostic accuracy of 78%–96% [16]. The overall agreement between the 2 studies was 91% and in 9% of renal units VUR was detected only on VUS making it the more sensitive study. Another potential advantage of the VUS as compared to RNC is the ability to grade VUR similar to the International Reflux grading system with a 75% concordance shown between the VUS and VCUG grading. The discordant findings are primarily because of a significant number of grade-1 VUR on VCUG being grade 2 or higher on VUS. The absence of radiation, the ability to evaluate the upper tracts simultaneously and its higher sensitivity make it an attractive tool for evaluating VUR. The potential drawbacks include inadequate evaluation of bladder and urethral morphology, higher costs of contrast agent, longer exam time, and its operator dependence. Transperineal US of the urethra as part of the VUS has been used reliably in a few studies to date but further evaluation of this technique is necessary before VUS can replace the VCUG as the first examination for VUR especially in boys [17]. At present, VUS has a role in followup examinations for VUR, for screening siblings and possibly as the first examination for VUR in girls.

2.4. MR voiding cystography (MRVCUG)

MR cystography involves intravesical administration of gadolinium with imaging using MR during filling and voiding. The relative benefits of the procedure are that it can evaluate VUR without ionizing radiation and additionally give important information about renal-acquired cortical defects and differentiate acquired cortical defects from congenital dysplasia. It must be borne in mind that dysplasia and scarring are different entities diagnosed on histopathological examination. In this paper we refer to them as congenital and acquired cortical defects. The potential drawbacks include a lower sensitivity as compared to VCUG, higher costs, and the need for sedation or anesthesia to perform the study. Takazakura et al. showed 90% sensitivity and a 96% specificity of MRVCUG and all children with grade 3 or more VUR were identified using this modality [18]. Lee et al. further correlated the MRVCUG findings with a DMSA SPECT scan to demonstrate the advantage of getting this additional information with a single test [19].

2.5. PIC cystogram

Rubenstein et al. in 2003 introduced a novel but controversial technique to identify VUR in children presenting with febrile UTIs and negative VCUG [20]. The authors performed the PIC (Positioning the Instillation of Contrast at the ureteral orifice) cystogram by positioning the cystoscope close to the ureteric orifice with the bladder empty and instilling contrast in gravity-aided manner from a height of 1 m using the irrigation port of the scope. The argument that this technique could induce VUR was countered by using a control group of children without UTI and VUR where the PIC cystogram also did not demonstrate reflux. In contrast, all children with febrile UTIs and no VUR on VCUG showed

VUR on the PIC cystogram. A multi-institutional study confirmed that PIC VUR could be demonstrated in 82% of children who present with febrile UTI and normal VCUG [21]. The inherent problem with both these studies has been the lack of standardization of the VCUG technique used, absence of upper tract imaging findings, and strict definition of UTI. This latter objection has been addressed in a more recent study by Tareen et al. who evaluated 5 children with recurrent febrile UTI and upper tract changes on DMSA/CT scan [7]. All 5 patients showed VUR on PIC cystography and went on to endoscopic or open VUR correction. The results of these studies indicate that the majority of children with febrile UTI and no VUR on a VCUG would have VUR on a PIC cystogram. Before adding this investigation as a routine modality for children with febrile UTI and negative VCUGs, further prospective randomized studies are indicated to define the population who would benefit from this intervention.

3. INDICATIONS FOR IMAGING FOR SUSPECTED VUR

The primary indications for evaluating children for VUR are discussed in this section. There has been considerable evolution of our knowledge about VUR management over the last several years. The role of antibiotic prophylaxis in preventing recurrent infections has been challenged along with an increasing awareness of the development of antibiotic resistance [1–3]. This coupled with identification of other stronger predicting factors for recurrent infection like lower urinary tract dysfunction (LUTS) has led to a more conservative approach in identifying and treating VUR [22]. This section suggests recommendations for the evaluation of children with suspected VUR.

3.1. Children with urinary tract infection

The American Academy of Pediatrics: Committee on Quality Improvement recommends a VCUG for all children aged between 2 months to 2 years old following the first febrile UTI [23]. The rationale for this practice is based on the traditional view that there is always uncertainty about whether previous infections were missed, high recurrence rates of UTI, high percentage of children with UTI having VUR and that the risk of renal-acquired cortical defects is highest in younger children. In practice, however, this recommendation is often not followed rigidly primarily because of poor documentation of significant bacteriuria and pyuria which puts in doubt the diagnosis of a UTI. For older children, age at presentation, gender, race, type (febrile or non febrile), frequency of UTI, and social factors must be considered before proceeding to a VCUG. Toilet-trained female children with cystitis are primarily evaluated by a full voiding diary and the dysfunctional voiding symptom score (DVSS) rather than a VCUG [24]. In children with recurrent cystitis a uroflowmetry and US are added. However, in the presence of a well-documented episode of PN or recurrent febrile UTI, a VCUG or RNC is warranted along with a US or DMSA scan to assess the upper tracts. All males with a well-documented febrile UTI should undergo a VCUG. Because of the well-documented low incidence of VUR in black children, a VCUG is not indicated for older black children presenting with UTI. The initial VCUG can be performed after the child is afebrile, clinically stable and the urine is sterile [25]. The dose of antibiotic prophylaxis is doubled a day before the test and continued at therapeutic levels for another day following the test.

3.2. Sibling VUR

Primary VUR is the commonest heritable disorder of the genitourinary tract and is inherited as a Mendelian dominant with partial expression [26]. Several studies on sibling VUR have identified factors, which can help predict the risk of sibling VUR. Hollowell in an analysis of 1768 siblings showed a mean VUR incidence of 32%, which was 44% in siblings less than 2 years of age as compared to 9% of siblings greater than 6 years [27]. If the sex of the sibling or proband is considered separately there is no statistical association. On the other hand, female siblings of the female index patient have a higher likelihood of VUR than their male counterparts [28]. Monozygotic twins have an obviously higher risk than dizygotic twins. Hollowell showed that approximately two-thirds of siblings have low grade (I, II) VUR and the spontaneous resolution rate is higher when compared to children diagnosed with VUR after a UTI [27]. Giel et al. presented the long-term outcome of asymptomatic siblings screened for VUR with an initial US [29]. Of the 117 siblings in this study, 11 (9.4%) had abnormal US findings, 5 of which showed VUR on a VCUG. In 85 siblings with an average followup of more than 8 years, none had complications of VUR. Other authors have argued for a more proactive approach in diagnosing VUR in siblings [30, 31]. Houle et al. demonstrated a 26% incidence of cortical defects in siblings and indicated that siblings screened after 2 years of age had a higher risk of renal damage [30]. The alternative argument here is that perhaps these findings represent congenital defects rather than acquired preventable defects.

A tailored approach for siblings therefore could be an RNC or a VUS in siblings younger than the toilet-trained age and US as the initial screening modality for all older siblings. In the presence of any US evidence of cortical damage a VCUG is recommended in children under 5 years of age as they form the subset most at risk of renal damage. Symptomatic siblings at any age are evaluated with a VCUG.

3.3. Prenatal hydronephrosis and VUR

VUR is suspected antenatally in the presence of ureteric dilatation and/or hydronephrosis (HN) or following the diagnosis of ectopic kidneys, multicystic dysplastic kidney, and unilateral renal agenesis wherein there is an increased incidence of contra lateral VUR. Van Eerde et al. performed a meta-analysis to review the value of antenatal HN in predicting postnatal VUR [32]. HN was defined as renal pelvic diameter more than 4 mm with or without caliectasis. Among the 1178 cases, the mean prevalence of primary VUR was 14.9%. When stratified by anteroposterior renal pelvic diameter (APD), VUR was diagnosed in 14% of infants with

APD ≤ 10 mm and in 12% of infants with APD ≥ 10 mm. It is known that a negative prenatal screening or a normal postnatal US in infants with antenatal HN does not rule out VUR. In a meta-analysis reported by Lee et al., the prevalence of VUR ranged between 4.4% and 14% [33]. There was no correlation between the degree of prenatal HN and the presence or grade of VUR. Similarly, in another study conducted on 108 children with antenatal HN, VUR was detected in 15% and there was no correlation between the degree of pelviectasis on postnatal US and the presence or severity of VUR [34]. Children with antenatal HN and VUR have a more benign course with a higher resolution rate when compared to children diagnosed with VUR following a UTI [35, 36]. Upadhyay et al. followed 25 children with antenatally detected HN and VUR [36]. Reflux was greater than or equal to grade III in 70% of children. VUR resolved in 52% and was downgraded in 24%. Breakthrough urinary tract infection occurred in 4 patients with grades IV and V reflux, and dysfunctional voiding developed in 5. Followup renal scans showed decreased differential function (mean 18%) in 2 units without new scars. A selective approach is advisable for investigating neonates with antenatal HN. If the renal size and parenchyma is unremarkable, it may be reasonable to reserve the VCUG for children with SFU grade 3-4 HN or bilateral HN and in the presence of ureteric dilatation.

3.4. Other situations

A routine VCUG is recommended in the work up of children with multicystic dysplastic kidneys (MCDK) based on the reported 15%–25% prevalence of VUR in children with MCDK [37–40]. Miller et al. found a 25% VUR rate in the contralateral kidney in 75 patients with MCDK [37]. In this series, about 50% of children with VUR had grades ≥3, 50% resolved spontaneously by 5 years of age and only 1 of the 75 children required surgical intervention for VUR. Guarino et al. documented that 16% of children with MCDK had VUR and the VUR grade was significantly higher in boys as compared to girls [39]. This finding was also noted in the study by Selzman and Elder, wherein 15% of children showed contralateral VUR, with the prevalence being higher in boys and the white population [40]. Ismaili et al. recommended that 2 successive normal US studies in the neonatal period identifie most significant contralateral anomalies avoiding the use of a routine VCUG [38]. In their study, 61 of the 76 newborns with MCDK had 2 normal neonatal US. Among them, 4 (7%) had low grade VUR which resolved spontaneously in all before 2 years of age. Further studies are needed to validate this finding before stopping routine VCUGs in children with MCDK.

The incidence of VUR in children with unilateral renal agenesis (URA) is slightly higher than MCDK and varies between 24%–28% [39, 41–43]. The VUR can be high grade and shows a lower spontaneous resolution rate as compared to MCDK [41]. Arena et al. evaluated 60 children with renal ectopia (crossed 24, simple 36) [44]. The authors recommended complete urological evaluation of children presenting with renal ectopia. The incidence of associated VUR was 37% with crossed ectopia and 17% with simple ectopia. Unlike MCDK, Guarino et al. noted that girls had a higher grade of VUR and lower resolution rates [39]. In view of the high incidence of neurogenic bladder dysfunction and VUR (20%–47%) children with anorectal malformation should also undergo a VCUG [45].

4. WHAT SHOULD THE FIRST INVESTIGATION FOLLOWING PYELONEPHRITIS BE: DMSA OR VCUG?

Primary VUR occurs in less than 1% of the general population but up to 50% of children who present with a UTI will have VUR [46]. Therefore, the detection of VUR is an abnormal finding. The primary reason for identifying VUR as a disease entity has been its association with pyelonephritis (PN), which, if recurrent, can lead to acquired cortical defects and subsequent hypertension and/or end stage renal failure. This perception that the triad of UTI-VUR-nephropathy is an intimate link has driven physicians to actively diagnose and treat VUR over the last 3 decades.

There is a considerable debate regarding the initial investigation following a febrile UTI with several studies highlighting the emerging role of DMSA scan vis a vis the VCUG. The rationale for this argument stems from the recent evidence which has downgraded the importance of VUR as a sole factor in causing long-term renal damage. In fact, our aggressive management of VUR over the last several decades has not impacted long-term renal outcome. Craig et al. reviewed the Australia and New Zealand Dialysis and Transplant Registry between 1971 and 1998 and noted that over the decades, despite a more aggressive identification and treatment of VUR, reflux nephropathy continued to remain a cause of ESRD in about 14% of children registered [47]. This section discusses this current thought process and refocuses our attention to our primary goal which is the identification of risk factors which lead to progressive renal damage.

4.1. Pyelonephritis and acquired cortical defects can occur without VUR

Recent studies have demonstrated that acquired renal scarring correlates best with recurrent UTI and not with VUR and primary VUR is neither sufficient nor essential for renal damage. The exception to this rule is secondary reflux associated with bladder outlet obstruction or high-pressure neurogenic bladders. Gordon et al. performed a meta-analysis to determine the value of VUR diagnosis to predict renal damage in children hospitalized with UTI [4]. The analysis evaluated 12 studies comprising 537 children with 1032 kidneys and showed that primary VUR was a poor predictor of renal damage on a DMSA scan in children hospitalized with UTI. A positive VCUG increased the chance of a positive DMSA scan by only about 20% whereas a negative VCUG increased the chance of negative DMSA scan by 8%. The authors concluded that the VCUG could not be used as a primary screening test to detect renal parenchymal damage in children with UTI. Taskinen and Rönnholm noted that fever more than 39°C,

Table 1: Results of studies analyzing concordance between DMSA and VCUG findings.

Study (N)	POS DMSA POS VCUG	POS DMSA NEG VCUG	NEG DMSA POS VCUG	NEG DMSA NEG VCUG
Hansson et al. (303)	53 (17%)	103 (34%)	27 (9%); ≥ III VUR in 7	120 (39%)
Tseng et al. (142)	37 (26%)	64 (45%)	5 (3.5%); ≥ III VUR in 0	36 (25%)
Preda et al. (290)	44 (15%)	105 (36%)	8 (2.7%); ≥ III VUR in 1	133 (46%)

CRP > 100 mg/mL, and proteinuria during UTI were predictors of renal damage [48]. The presence of VUR did not increase the risk of renal defects on DMSA scanning. On followup, DMSA scans 2 years following UTI, 9 of the 12 patients who showed evidence of cortical defects did not have associated VUR.

4.2. Cortical defects in children with VUR predicts recurrent infection

Mingin et al. retrospectively reviewed records of children who underwent DMSA scans following a febrile UTI or antenatal HN [49]. 88% of the children with an abnormal DMSA scan had grade 3–5 VUR. Of the 51 children with an abnormal DMSA and grade 3–5 VUR 60% had a subsequent breakthrough UTI. In comparison, only 6% of children with similar VUR grade and a normal DMSA scan developed breakthrough infection. Furthermore, only 5% of children with an abnormal DMSA scan showed improvement in VUR grade on followup as compared to a 46% resolution rate in those without DMSA abnormality, a fact only partly attributable to the lower initial grade of VUR in this subset.

4.3. A positive DMSA scan identifies significant VUR in most instances

In 303 children less than 2 years of age evaluated with VCUG and DMSA scans after an episode of UTI, Hansson et al. found that 51% had an abnormal DMSA scan and 46% with a positive DMSA scan had no evidence of VUR on VCUG [50]. There was a significant association between ≥grade III VUR and DMSA positive renal lesions. A normal DMSA scan and dilating VUR were found in only 7 children in this study, of which only 1 showed a scarred kidney on followup. None of the 7 children had recurrent UTI on followup. The authors suggested that DMSA could replace VCUG as the primary evaluation for children following a UTI. VCUGs could be selectively performed in children with abnormalities on DMSA scans and this would reduce the number of VCUGs by about half based on the results of this study. The same group conducted a further prospective study to test this hypothesis [51]. In 290 children with UTI in infancy, 52 had VUR which was dilating in 27. An abnormal DMSA scan was documented in 26 of the 27 children with dilating VUR. Tseng et al. also attempted to answer this question whether a normal DMSA can obviate the need for a VCUG following the first UTI [52]. In 142 children, only 5 children with a normal DMSA scan had VUR (all less than or equal to grade 2) and no child with dilating reflux had a normal DMSA scan. Table 1 summarizes these results.

4.4. Antibiotic prophylaxis does not prevent recurrent UTI in children with low-grade VUR

The role of VUR, especially lower grades, as a predisposing factor for recurrent UTI is also controversial. Nuutinen and Uhari noted a higher rate of recurrent UTIs in children with grade III–V VUR in comparison with children with grade I-II VUR [53]. It is now believed that the susceptibility for recurrent UTI is more related to a defective urothelial defense mechanism and bladder dysfunction rather than associated VUR. Roussey-Kessler et al. conducted a prospective study on children with grade 1–3 VUR randomized to receive cotrimoxazole or no treatment with UTI on followup as an end point [3]. There was no significant difference in the occurrence of UTI in both groups except in boys with grade 3 VUR ($P = .04$). Garin et al. performed a randomized prospective trial in 218 children with or without VUR who presented with PN, comparing prophylaxis with no prophylaxis [2]. The study only included patients with grade I–III VUR. No statistically significant differences were found among the groups with respect to the rate of recurrent UTI, type of recurrence, rate of subsequent pyelonephritis, and development of renal parenchymal scars. The overall rate of recurrent PN in this study was 5.5% and VUR did not increase the likelihood of PN. The authors concluded that at 1-year followup, grade I–III VUR did not increase the incidence of UTI, PN, or cortical defects. Conway et al. performed a time-to-event analysis on 611 children who are presented with the first UTI to determine the association between antibiotic prophylaxis and recurrent UTI and to identify risk factors for resistance [54]. The factors associated with an increased risk of recurrent UTI in this study were white race, age between 3–5 years, and grade IV-V VUR. Sex and grade I–III VUR were not associated with the risk of recurrence. Moreover, antibiotic prophylaxis was not associated with a decreased risk of recurrent UTI in a multivariable analysis but was a risk factor for antibiotic resistance among children with recurrent UTI.

The problem in interpreting studies attempting to clarify this aspect is the lack of a standardized definition of a febrile UTI and the variability in the methodology of obtaining urine samples. The ongoing randomized intervention for children with vesicoureteric reflux (RIVUR) study is a multicenter, double blinded, randomized, placebo controlled trial which aims to answer the ongoing controversy regarding the role of antibiotic prophylaxis in preventing recurrent

febrile/symptomatic UTI in children with VUR diagnosed after a UTI.

In summary:

(1) in children presented with a UTI, up to 50% of children may have evidence of upper tract damage without evidence of VUR on a VCUG;

(2) the rate of spontaneous resolution of VUR is higher in children with low-grade VUR and a normal DMSA scan;

(3) a positive DMSA scan at diagnosis predicts a higher rate of recurrent UTI or breakthrough infections in children with VUR;

(4) VUR identification has not altered the ESRD rate related to reflux nephropathy.

The idea behind these studies is to encourage a more selective approach in investigating children who present with a first UTI, contrary to the AAP practice guidelines. A DMSA would be the initial investigation and all children with an abnormal DMSA will then proceed to a VCUG. This would identify the majority of children with dilating/significant VUR who would then benefit from antibiotic prophylaxis, thus reducing both the number of VCUGs and number of children on antibiotic prophylaxis. Such a selective approach is justifiable with one objection being that boys with a potential posterior urethral valve presented outside the neonatal period may be missed with this approach. However, this may be unlikely if a US study is simultaneously performed as part of the routine work up.

4.5. MR urography (MRU)

MRU is increasingly being advocated as a single imaging modality, which can be used to provide information obtained on a VCUG and DMSA scan. The primary advantage of the MRU is its ability to distinguish between renal dysplasia (congenital cortical defects) and acquired scarring (acquired cortical defects) [55]. In addition to morphological analysis, MRU can provide information about renal perfusion, concentration, and excretion of contrast media by calculating the renal and calyceal transit times. The Patlak differential function and the calculated Patlak number per mL of renal tissue is considered a surrogate for the single nephron GFR and can therefore serve as an important tool in prognosticating and following children with renal dysplasia.

5. FOLLOWUP IMAGING FOR VUR

The ALARA (as low as reasonably achievable) concept has stressed the importance of minimizing radiation exposure in children being followed conservatively after diagnosis of VUR [5]. Thompson et al. devised a theoretical model to study this and conducted a retrospective study in children with primary VUR diagnosed after a UTI to evaluate different strategies of followup and its effect on antibiotic exposure and cost [56]. The authors recommended that children with mild VUR undergo a VCUG every 2 years whereas those with moderate to severe VUR should undergo a VCUG every 3 years. In a survey of the members of the American Association of Pediatrics published in 2001, 99% of the respondents indicated that they would perform a VCUG or RNC every 12–18 months in followup [57]. The current followup protocol should aim to reduce the number of VCUG/RNC performed while children are on antibiotic prophylaxis basing it on the natural resolution decay curve of VUR. It is accepted that all subsequent followup studies following a VCUG should be an RNC.

5.1. Factors identified on imaging which predict VUR resolution

Persistence of VUR is more likely in high-grade VUR, in children with bilateral disease (especially in Grade IV and V) and when reflux is diagnosed in the older child. The value of the VCUG and RNC in predicting VUR resolution has been studied. It has been demonstrated that when VUR occurs at less than 60% of expected bladder capacity and the reflux volume is more than 2% of bladder capacity, the resolution is poor [58, 59]. Knudson et al. on a multivariate analysis stated that bladder volume on initial cystogram of greater than 50% of predicted bladder capacity, age younger than 2 years at diagnosis, and a history of prenatal hydronephrosis were significant factors predicting VUR resolution within 2 years [35].

6. CONCLUSION

VUR is a heterogenous disorder, and its diagnosis and management continues to remain one of the most controversial problems in pediatric urology. There is a realization that rather than a disease entity, VUR is a marker of overall urinary tract dysfunction, which may predispose to UTI. The primary goal for the treating physician should continue to remain preservation of renal function and preventing the relatively small percentage of acquired renal defects associated with VUR. There has been a paradigm shift in the earnestness with which the diagnosis of VUR is sought after based on an increasing body of evidence which suggests that acquired renal defects are often not related to VUR and that our current modalities for diagnosing VUR are associated with unacceptable radiation exposure and bladder catheterization. The newer modalities do hold promise but further work is warranted before they can replace the existing well-established techniques.

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Review Article

Anxiety in Children Undergoing VCUG: Sedation or No Sedation?

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Background. Voiding cystourethrograms are distressing for children and parents. Nonpharmacological methods reduce distress. Pharmacological interventions for VCUG focus on sedation as well as analgesia, anxiolysis, and amnesia. Sedation has cost, time, and safety issues. Which agents and route should we use? Are we sure that sedation does not influence the ability to diagnose vesicoureteric reflux? *Methods*. Literature search of Medline, EMBASE, and the Cochrane Database. Review of comparative studies found. *Results*. Seven comparative studies including two randomised controlled trials were reviewed. Midazolam given orally (0.5-0.6 mg/kg) or intranasally (0.2 mg/kg) is effective with no apparent effect on voiding dynamics. Insufficient evidence to recommend other sedating agents was found. Deeper sedating agents may interfere with voiding dynamics. *Conclusion*. Midazolam reduces the VCUG distress, causes amnesia, and does not appear to interfere with voiding dynamics. Midazolam combined with simple analgesia is an effective method to reduce distress to children undergoing VCUG.

1. INTRODUCTION

The voiding cystourethrogram (VCUG) is the gold standard for diagnosing vesicoureteric reflux (VUR) and a number of other bladder conditions [1, 2]. The VCUG is a procedure performed mainly on infants and young children in the Radiology Department [3]. There is increasing belief that interventions for VUR are less effective than anticipated, but much debate remains [4–11]. The child is required to be conscious, a urinary catheter is inserted, and the bladder is filled with radio-opaque material, then the child is asked to spontaneously void [12]. This procedure creates distress in the child, the parents, and occasionally staff [13–15]. Nonpharmacological methods to reduce this distress include education prior to the procedure, distraction during, and rewards after [14, 16–28].

Pharmacological interventions primarily focus on sedation but also could include beneficial analgesic, anxiolytic, and amnesic effects [29, 30]. Sedation brings with it cost, time, and safety concerns [1, 29–33]. It is unknown whether we can predict which children will go on to have distress or whether we should sedate routinely [34]. Which agents should we use, and what is the best route of administration? The majority of children having VCUG would not have had one previously. Coping styles and parent-child interaction are important determinants of distress during a medical procedure [34]. Safety of sedating agents is excellent in the context of a sedation service with the necessary staff and equipment to manage sedation in young children [35–37]. Those who sedate children should be prepared for inadvertent deeper sedation, basic life support, and airway management [29–31, 38–40]. Advanced help should be available. Time and cost factors limit the introduction of this distress-reducing intervention. Sedation recovery area and staff time are being the primary cost factors. The medications themselves are relatively inexpensive. Finally, are we sure that sedation does not influence the VCUGs ability to diagnose vesicoureteric reflux?

2. METHODS

These methods include a sensitive search of PubMed (1950–2007), EMBASE (1980–2007), Cochrane Database of Systematic Reviews, and Cochrane Randomised Controlled Trials Register. Articles on VCUG were identified through the terms urography (MESH heading exploded), micturating, or voiding cystourethrogram using wildcard search for variations of spelling. Acronyms VCUG and MCUG were also used. To identify sedation articles, the following exploded MESH terms were used: "hyponotics and

sedatives," conscious sedation, midazolam, propofol, chloral hydrate, and nitrous oxide. "Sedation" was searched for as a title word. Results of the VCUG search and sedation search were combined. There were no limits on language for search, but only English language articles were reviewed. Further studies were identified from bibliographies. Unpublished studies were not actively sought.

3. RESULTS

Medline search (2008) found 234 papers of which 17 were considered to be of interest [6, 8, 13, 14, 16, 41–52]. EMBASE search found 416 papers of which additional 8 papers were of interest [27, 35, 53–59]. Cochrane Randomised Controlled Trials Register found no further articles of interest. Cochrane Database of Systematic Reviews found one review on interventions for primary vesicoureteric reflux, but none on sedation for this procedure [7]. A review of the bibliographies identified further 39 papers of interest [2–5, 9, 11, 15, 17–22, 26, 28, 34, 37, 40, 60–81]. Four papers on anesthesiology for VCUG were found and included for discussion [82–85].

Any study comparing a sedative against another sedative, placebo, or standard treatment for VCUG was reviewed. One French language article [77] and one Polish language article [56] were not included. Study designs are summarised in Table 1. Outcome measures and results are in Table 2 [41, 43, 45, 47, 52, 59]. Quality assessment is shown in Table 3. Only two of the studies [45, 52] were of high quality with Jadad scores [86] of 4 or more. One unpublished comparative study was found, but not included [68].

4. DISCUSSION

The best way to avoid the distress of the VCUG is not to do the procedure. A better way to image vesicoureteric reflux has recently been discussed in an editorial by Elder [55]. As much evidence becomes available to show that we are not influencing the outcome of VUR, less VCUGs may be ordered [7, 93]. Possible alternatives include Doppler ultrasound [94] or ultrasound with contrast [61]. A suprapubic approach to avoid catheterisation seems promising but still requires filling and voiding [49]. Methods to detect reflux without voiding are impaired as some reflux may be present only on voiding [95], although the fact that whether this is important or not is debated [96]. Nuclear medicine scanning may be an alternative or may be able to select those who are more likely to benefit from VCUG [67]. Nuclear medicine cystoscopy replaces radio-opaque contrast with pharmacolabelled material with lower radiation, but otherwise it is very similar to the VCUG. Currently, VCUG remains the gold standard until less invasive tests are developed [1]. At the very least, we should be perfecting our current technique [12].

5. DISTRESS, PAIN, AND ANTICIPATORY ANXIETY

Distress is an all encompassing term that may or may not include a painful stimulus. This can be evidenced by fear of a procedure, pain responses prior to nociceptive stimuli, or anxiety behaviours before a planned event. Distress during the voiding cystourethrogram has been reported in observational and controlled studies. Phillips et al. [13] showed that 52 out of 73 children (71%) experienced serious distress, severe distress, or panic on the Groningen distress rating scale [90]. Herd et al. found that serious or severe distress was detected in 61% of all unsedated children at some stages during the VCUG. This level of distress may have been brief but is generally considered unacceptable. This distress is caused not only by urethral catheterisation, but also by the distension of the bladder and the subsequent voiding of urine in a socially abnormal situation (Figure 1). Nociceptors related to urethral mucosa and stretch receptors in the bladder provide the peripheral pain signals, but the majority of the distress is cortical.

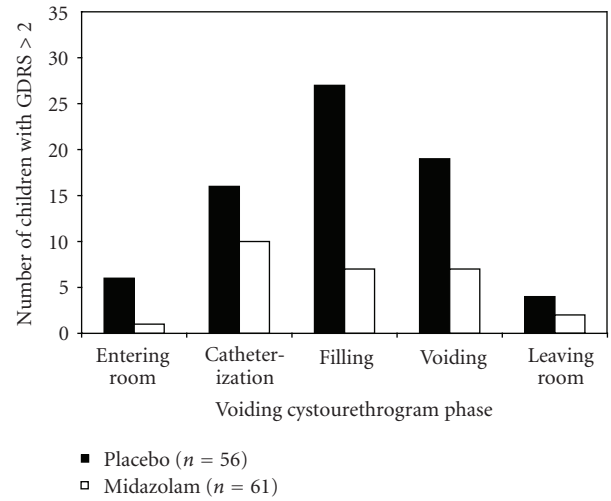

Figure 1: Bar graph shows the number of children (n = 117) who experienced serious or severe distress (Groningen distress rating scale (GDRS) score >2 [90]) at each phase of voiding cystourethrography. 56 received placebo (black bars) and 61 received midazolam (white bars), from [45].

Distress can also be manifest in the parent. Parents' perceptions of fear, distress, and pain in their children are anticipated to be greater than the reality [51].

6. PSYCHOLOGICAL THERAPY (NONPHARMACOLOGICAL TREATMENTS)

Psychological treatments should be considered first as they often have little or no risk. There are many ways to reduce the distress of procedures in children [19] and even more challenges researching and implementing psychological interventions for controlling children's pain [97]. Interventions may range between simple educational [28] and more structured play therapy sessions [14, 76] and hypnoses [42]. Preparation, distraction, and reassurance before, during, and after the procedure are likely to reduce the distress of the procedure [22, 69, 75]. Parental presence is comforting for children during painful procedure and should be encouraged despite the lack of specific VCUG evidence [23].

Table 1: Studies comparing a sedative against another sedative, placebo, or standard treatment for VCUG. Design and interventions. (NSD: no significant difference; VCUG: voiding cystourethrogram; RNC: radionuclide cystography; VUR: vesicoureteric reflux; SD: standard deviation).

Authors; year; country	Title	Patients	Intervention and comparison	Nonpharmacological cointervention	Time of follow-up and differences (if any)
I. Akil, M. Ozkol,O. Y. Ikizoglu, M. Polat, O. Y. Tuncyurek, O. Taskin, H. Yuksel; 2005; Turkey [41]	"Premedication during micturating cystourethrogram to achieve sedation and anxiolysis"	53 (39F;14M), >6 m, median age of 6 y (range from 7 m to 11.1 y); first VCUG 98%	Oral *midazolam* of 0.6 mg/kg (max. of 15 mg) versus *chloral hydrate* of 25 mg/kg (max. of 500 mg) versus *Placebo*; 15–30 min prior to VCUG	Parents informed about MCUG and permission granted for sedative drug and making child nil by mouth for 3 h, parental presence not stated	Until they were allowed to drink clear liquids, usually 1 h after completion of the procedure
J. S. Elder, R. Longenecker; 1995; USA [43]	"Premedication with oral midazolam for voiding cystourethrography in children: safety and efficacy"	98 children previously distressed by VCUG (38) or appeared shy (79F;19M), mean age of 4.4 (range from 23 m to 9 y); 25 controls (21F : 4M), mean age of 4.6 (range not stated); first VCUG 61%	Oral *midazolam* of 0.6 mg/kg (max. of 15 mg), 20–30 min prior to VCUG or NUC versus *standard care*	Parents of intervention group-contacted prior with purpose of midazolam and expected effects, parents are allowed to be present	Phone call at 48 h
D. W. Herd, K. A. McAnulty, N. A. Keene, D. E. Sommerville; 2006; New Zealand [45]	"Conscious sedation reduces distress in children undergoing voiding cystourethrography and does not interfere with the diagnosis of vesicoureteric reflux: a randomized controlled study"	Children of 1–14 y (eligible); 139 randomised, 117 completed VCUG on the day (84F : 33M), 8 had VCUG completed later, age >1 y, mean ages of 3.6 y (SD1.8) and 3.4 y (SD2.1), ASAI-II	Oral *midazolam* of 0.5 mg/kg (max. of 15 mg), 30 min prior to catheter insertion versus *placebo*	All offered play therapy (visit to department, doll catheterised), four-page pamphlet, only the treatment group fasted for 6 h with solids and 4 h with liquid (i.e., control group was allowed to eat), parent/caregiver present, skilled nurse did all catheters	60–90 min after medication
I. Keidan, R. Zaslansky, M. Weinberg, A. Ben-Shlush, J. M. Jacobson, A. Augarten, Y. Mor; 2005; Israel [47]	"Sedation during voiding cystourethrography: comparison of the efficacy and safety of using oral midazolam and continuous flow nitrous oxide"	47 (42F : 5M), age of 3–16 y, ASAI and II, mean age of 6 (range from 3 to 15)	Oral *midazolam* of 0.5 mg/kg (max. of 15 mg), 20 min prior to procedure versus continuous flow *50% nitrous oxide*	Both groups fasted with solids for 6 h, and liquids for 2 h, parents were encouraged to accompany the children throughout the procedure, flavoured nasal mask was used for nitrous oxide	24 h follow-up by telephone, recovery time of 63 min (SD 25) in midazolam group, 29 min (SD 10) in the N2O group ($p < .001$)
P. A. Merguerian, S. T. Corbett, J. Cravero; 2006; USA [48]	"Voiding ability using propofol sedation in children undergoing voiding cystourethrograms: a retrospective analysis"	544 charts, 287 selected ages from 2 to 8 (preselected), mean age of 51 m (244F : 43M), first VCUG 75%	Sevoflurane induction followed by *propofol* infusion on its own (*historical controls*)	Not reported	

Table 1: Continued.

Authors; year; country	Title	Patients	Intervention and comparison	Nonpharmacological cointervention	Time of follow-up and differences (if any)
E. Stokland, S. Andréasson, B. Jacobsson, U. Jodal, B. Ljung; 2003; Sweden [52]	"Sedation with midazolam for voiding cystourethrography in children: a randomised double-blind study"	Children of 0.5 to 9 y (eligible), 95 enrolled (70F : 20M), gender stratified, median age of 2.2 y, midazolam, 3.2 placebo	Intranasal *midazolam* of 0.2 mg/kg (max. of 5 mg), 3–5 min prior to bladder catheter versus *placebo*	Oral and written information	Follow-up questionnaire and phone call at 48 h
J. L. Zier, K. A. Kvam, S. C. Kurachek, M. Finkelstein; 2007; USA [59]	"Sedation with nitrous oxide compared with no sedation during catheterization for urologic imaging in children"	Children of 4–18 y selected by investigator undergoing VCUG or RNC, enrolled 204 (165F : 39M) out of 389, mean age nonsedated: 6.4 (range of 4–15.2), sedated: 6.3 (range of 4–14.9)	Continuous flow *70% nitrous oxide* until catheterisation is complete versus *standard care*	All patients fasted for 4 h	To time of discharge, longer in sedated group, 85 min versus 33 min ($P < 0.001$)

Those who have been previously distressed by VCUG would seem to be ideal candidates for sedation, but the majority of children would not have had a previous VCUG. Factors which may reduce distress in children during VCUG include "effortful control" by the child and coping and distress-promoting behaviours by the parent [34]. No validated prediction tool exists for VCUG distress.

7. PHARMACOTHERAPY

Pharmacotherapy includes sedation, anxiolysis, analgesia, amnesia, and anesthesia.

7.1. Sedating agents

Sedation continues to be difficult to define[63]. In the case of the VCUG, a degree of consciousness is required. This may be defined as light sedation, and the use of oxymoron "conscious sedation" is being discouraged [98].

Midazolam

Of the selected studies, 5 had midazolam as a treatment arm and 4 of which were oral and one intranasal. Oral midazolam dose was 0.5 mg/kg in two studies [45, 47] and 0.6 mg/kg in two other studies [41, 43]. Maximum dose was 15 mg in all. Time between ingestion and procedure ranged from 15 to 30 minutes. Intranasal dose in one study was 0.2 mg/kg with a maximum of 5 mg, and it was administered 5 minutes before the procedure [52]. A number of behavioural measures were employed (Table 1). All the studies demonstrate significantly less distress with midazolam in a variety of measurement tools. Few adverse effects were encountered. Midazolam may cause adverse paradoxical agitated reactions in less than 5% of children [99]. These reactions have been shown in case reports to be ameliorated using the antidote for midazolam (flumazenil) both in adults [100] and children [101]. Ketamine, a dissociative anesthetic, has been shown to be more effective than increased doses of midazolam or placebo in a randomised controlled trial [99].

The study by Stockland et al. [52] on 95 children compared intranasal midazolam (0.2 mg/kg with a maximum of 5 mg) to placebo. Nurses reported a trend to easier procedure in the midazolam group ($P = .07$), with girls reported easier than boys ($P = .06$). No serious adverse events were reported. Parents felt that the administration of midazolam was more uncomfortable than that of placebo ($P < .001$). Parents felt that midazolam made catheterisation, voiding, and the overall procedure more comfortable ($P = .015$, $P = .08$, and $P = .047$, resp.). The authors report P-values and no absolute scores, which makes it impossible to estimate treatment effect size or clinical relevance.

A study by the current author and colleagues [45] compared oral midazolam (0.5 mg/kg with a maximum of 15 mg) to placebo in 125 children who had VCUG. Behavioural observations were completed in 117. This was the only study that calculated a priori power requirement or attempted to quantify the treatment effect. We rated our paper highly using the Jadad score [86]. We found no serious adverse events. The number of children experiencing serious or severe distress (Groningen distress rating scale (GRDS) >2) at any stage of the procedure was 34 (61%) in the placebo group and 16 (26%) in the midazolam group. Number needed to treat to reduce serious or severe distress in one child was 2.9 (95%CI 1.9–5.5). VUR was identified in 16% of all children. This study was limited to children above the age of one year.

Table 2: Studies comparing a sedative against another sedative, placebo, or standard treatment for VCUG. Outcomes, results, and follow-up. (NSD: no significant difference; VCUG: voiding cystourethrogram; RNC: radionuclide cystography; VUR: vesicoureteric reflux; SD: standard deviation).

Authors; year; country	Sedation score outcome and results	Distress outcome(s) and results	Urological outcome(s) and results	Safety outcome(s) and adverse events
I. Akil, M. Ozkol, O. Y. Ikizoglu, M. Polat, O. Y. Tuncyurek, O. Taskin, H. Yuksel; 2005; Turkey [41]	Breitkopf and Buttner classification of emotional status [87], 1.87 (SD0.72) in midazolam versus 1.35 (SD0.49) in control ($P = .01$), duration of sedation is 68 min (midazolam), 28 min (chloral), $P < .001$	Frankl behaviour rating score [88] NSD; Spielberger's state anxiety inventory [41] NSD; Houpt behaviour scale [88] of 4.93 (SD1.12) in midazolam group versus control of 4.12 (SD 1.05) in chloral group, all NSD	Postvoid residual volume, VCUG grading, no difference found	None found, defined as drop in PaO2/Sats by 5%, systolic blood pressure drop of 15 mm Hg, drop in pulse to 60 bpm
J. S. Elder, R. Longenecker; 1995; USA [43]	None	Phone call at 48 h, recall, behavioural side effects; parental wishes, 97 out of 98 contacted, 56 children (60%), no recall of VCUG, 19 (21%) recalled parts, 10 remembered the procedure without negative experience, 9 recalled a negative experience, 12 out of 97 children had behavioural side effects reported after the study, 92 out of 97 (95%) parents of sedated children would request the use of midazolam again	Postvoid residual volume (Bis and Slovis method [89]), no residual volume in 74% of midazolam group and 72% of control group; NSD	Saturation decrease by 10%, systolic BP drop by 15 mm Hg, respective rate down to 8/min, HR down to 60/min, one child had a transient decrease in saturation requiring no intervention
D. W. Herd, K. A. McAnulty, N. A. Keene, D. E. Sommerville; 2006; New Zealand [45]	None	Independent observer Groningen distress rating scale [90]; nursing GDRS; heart rate; parent-child interaction, 61% of placebo group experienced serious or severe distress (GDRS of 3 or 4); 26% of midazolam group had the same distress; number needed for treatment was 2.9 (95%CI 1.9–5.5)	VUR grade; volume infused, no difference in volume infused ($P = .8$), no difference in VUR grading ($P = .31$), a priori power of 90%	Oxygen requirement (Sats <94%), two children in midazolam group had transient desaturations to less than 94% and were given oxygen

Nitrous oxide (N_2O)

Two studies evaluated nitrous oxide given with continuous flow devices at 50% and 70%. Keidan et al. compared 50% nitrous oxide in 23 children to 0.5 mg/kg oral midazolam in 24 children without a placebo group [47]. They found no difference between midazolam and 50% nitrous oxide although they did not design this as an equivalence study, and no power calculation was done. There was a trend for the time to micturition to be longer in the nitrous group

Table 2: Continued.

Authors; year; country	Sedation score outcome and results	Distress outcome(s) and results	Urological outcome(s) and results	Safety outcome(s) and adverse events
I. Keidan, R. Zaslansky, M. Weinberg, A. Ben-Shlush, J. M. Jacobson, A. Augarten, Y. Mor; 2005; Israel [47]	AVPU (alert, responds to voice, responds to pain, unresponsive)	FLACC (face, legs, activity, crying, consolability) score for pain [91]; anxiety score (observer scale of behavioural distress) [92]; no difference between midazolam and nitrous oxide, number of children requiring physical restraint is 10/24 in midazolam and 2/23 for N2O ($P = .01$)	Time to micturition 7.2 (SD2.5) min for midazolam and 15.3 (SD 17.3), $P = .8$	Oxygen saturation <93%, alteration in heart rate or BP by 15% from baseline, oversedation defined as "U" on the AVPU scale
P. A. Merguerian, S. T. Corbett, J. Cravero; 2006; USA [48]	Not reported	None	Void to completion; sedated children (55%) could void to completion compared to 89% nonsedated ($P < .001$)	Not reported
E. Stokland, S. Andréasson, B. Jacobsson, U. Jodal, B. Ljung; 2003; Sweden [52]	None	VAS from 0 mm to 100 mm (severe problems); nurse observation VAS NSD, parent VAS, administration of midazolam more uncomfortable ($P < .001$), catheter, and overall procedure more uncomfortable with placebo ($P < .001$); parent follow-up questionnaire at 12, 24, and 48 h of "reactions," NSD	VUR grade; volume infused; ability to void; NSD	Not defined, none reported
J. L. Zier, K. A. Kvam, S. C. Kurachek, M. Finkelstein; 2007; USA [59]	None	Brief behavioural distress score (BBDS) for VCUG, median age of 44 (range of 11–100) nonsedated, 11 (range of 0–67) sedated ($P < .001$), patient self-reported Wong-Baker FACES pain rating scale, 6 after catheter in nonsedated, 0 in sedated ($P < .001$)	Time to bladder emptying; NSD	One patient in sedated group experienced nausea, no desaturations

(15.3 minutes versus 7.2 minutes), but it did not reach statistical significance ($P = .08$). Nitrous oxide was significantly faster with regard to recovery time, with recovery in 29 minutes versus 63 minutes ($P < .001$). Zier et al. used 70% continuous nitrous oxide only for urethral catheterisation phase of VCUG in an older group of 107 children, and compared this to standard treatment in other 107 children [59]. The authors chose not to randomise the study based on difficulties with recruitment and parental expectations. Brief behavioural distress scores (BBDSs) were demonstrated

Table 3: Quality assessment of studies of sedation for VCUG, including Jadad score [86].

Authors; year; country; reference	Randomised	Randomisation described	Blinded	Allocation concealment	Withdrawals and dropouts?	Control	Placebo group	A priori power	Jadad score [86]
I. Akil, M. Ozkol, O. Y. Ikizoglu, M. Polat, O. Y. Tuncyurek, O. Taskin, H. Yuksel; 2005; Turkey [41]	Quasi	Y	Y (not described as double blind)	Cherry-flavoured liquid	N	Y	Y	N	1 (poor)
J. S. Elder, R. Longenecker; 1995; USA [43]	N	—	N	Kool-aid (artificial sweetner)	N	Y	Y	N	0 (poor)
D. W. Herd, K. A. McAnulty, N. A. Keene, D. E. Sommerville; 2006; New Zealand [45]	Y	Y	Y (blinding analysis done)	Mango and orange juices	Y	Y	Y	Y; 80% for GDRS; 90% for VUR grade	5 (excellent)*
I. Keidan, R. Zaslansky, M. Weinberg, A. Ben-Shlush, J. M. Jacobson, A. Augarten, Y. Mor; 2005; Israel [47]	Y	N	N	—	N	Y	N	N	1 (poor)
P. A. Merguerian, S. T. Corbett, J. Cravero; 2006; USA [48]	N	—	—	—	—	Y (historical)	N	N	0 (poor)
E. Stokland, S. Andréasson, B. Jacobsson, U. Jodal, B. Ljung; 2003; Sweden [52]	Y	Y	Y	Described	N	Y	Y	N	4 (good)
J. L. Zier, K. A. Kvam, S. C. Kurachek, M. Finkelstein; 2007; USA [59]	N	—	N	—	Y	Y	Y	N	1 (poor)

* Authors' self-score.

by the observational tool selected[102]. Wong-Baker FACES scale was the self-report tool used [103]. For the VCUG group ($n = 101$), BBDS was 44 (range of 11–100) in the nonsedated group versus 11 (range of 0–67) for the sedated group ($P < .001$). Immediately after catheterisation, the Wong-Baker FACES scale median was 6 for the nonsedated group and 0 for the sedated group ($P < .001$). Both studies reported time of completion, but neither study reported VUR grading or residual volume.

Other agents

Choral hydrate was compared to oral midazolam and placebo in one study [41]. A dose of 25 mg/kg was not found to be statistically different from placebo in reducing distress. This may have been due to inadequate dose or lack of power in the study. The sedation scale was also not significant for chloral versus placebo and, therefore, it suggests too low a dose was selected. There is no enough data to make any assessment of effect on voiding dynamics.

One retrospective study of propofol using historical controls was selected for review [48]. While this was an attempt to create a sedative state using low-dose propofol, the study required the presence of an anesthetist. During this study, low-dose propofol infusion followed sevoflurane gas induction and intravenous cannula insertion. This study found that propofol reduced the ability of children to completely void, which may interfere with the diagnosis of VUR.

7.2. Anxiolysis

Midazolam in the doses used in the reviewed studies is anxiolytic. Many children may appear fully conscious yet more cooperative, while another child given the same dose may appear sleepy. Where anxiolysis ends and sedation begins is unclear, but there would be a large overlap.

7.3. Analgesia

There is a wide range of analgesics available for children [104]. Midazolam does not provide any analgesia and, therefore, should be supplemented with a simple analgesic.

Acetaminophen

Acetaminophen is the most commonly provided childhood analgesic with low side effects and cost. It is routinely offered prior to other potentially painful procedures in children such as vaccination. Acetaminophen is usually provided in a sweet syrup base, and could be used to disguise the bitter taste of midazolam. There are many formulations of acetaminophen syrup, and palatability may vary [105].

Oral sucrose

Oral sucrose is an effective analgesic in new-born babies, and has been subject to several controlled trials and a Cochrane review [106]. While no studies have examined its effect for VCUG distress, it seems a simple likely effective intervention with low risk for children under 3 months of age.

Nitrous oxide

Nitrous oxide is a strong analgesic antagonising central NMDA receptors, and this is a potential advantage over midazolam. Study of Keidan et al. comparing midazolam to continuous flow nitrous oxide found no difference in FLACC scores [91], a measure of pain used more recently for procedural distress [107]. Study of Keidan et al. was not designed as an equivalence study, and no power calculations were done; so a true difference may not have been detected by the study.

Opiates

No studies have looked at opiate use for VCUG distress. Intranasal midazolam has proven effective, and opiates may also be administered by this route. Intranasal fentanyl shows promise as a rapid, easy-to-administer analgesic for severe pain in the children's Emergency Department [108]. Opiates may interfere with bladder function [109].

Local anesthetics

Lignocaine gel has been shown to reduce the pain of catheterisation for VCUG, but a 10-minute process of repeated application of lignocaine gel to the urethral meatus is required. The authors did not measure the effect of this procedure but only the reduced pain of catheterisation that followed. It would seem reasonable to use it with low risk of harm but at added cost [66]. Further study on children is required.

7.4. Anesthesia

There is increasing use of deeper sedation outside the operating room by nonanesthesiologists [110]. There is debate about which agents should be used outside the operating room and who should provide this service [63]. For VCUG, anesthetics have been given to avoid the trauma associated with urethral catheterisation, and then the child is allowed to wake and complete the VCUG. This does not avoid the distress caused by bladder distension or micturition. It also requires an anesthetist and the full costs associated with anesthesia and recovery.

8. WHO SHOULD RECEIVE SEDATION?

Many children do not experience distress during the VCUG. This may be related to previous experience, coping style, parental influence, staff skill, and empathy. Developmental considerations and education level of the child and parent are important. Nevertheless, many children, who would not have been predicted, may go on to experience distress. Parental perceptions of the procedure are such that most parents would request some medication if it were effective, safe, and available [43, 47].

9. DOES SEDATION AFFECT THE ABILITY OF THE VCU TO DIAGNOSE REFLUX?

Effect of sedation on ability to void can be measured with indirect or direct measures. Indirect measures include filling volume, residual volume, and time of micturition. Bozkurt et al. carefully examined urodynamic variables under the influence of midazolam [62]. They used a high-intranasal dose of 0.5 mg/kg. Stockland et al. used intranasal midazolam at a dose of 0.2 mg/kg, and found no difference in reflux grading between the groups [52]. They did not perform a power calculation, so there is still the possibility of missing a true effect. Herd et al. considered a clinically important difference in VUR to be a true shift of one grade down by half of the subjects with the use of midazolam [45]. It was important to detect a difference, so a 90% power was used. There was no difference in VUR grading between the groups (nonlinear mixed model analysis, $P = .31$). There was no evidence of a difference in volume infused between the two groups ($P = .8$).

10. CONCLUSIONS

Sedation reduces distress of the micturating cystourethrogram in children previously distressed or likely to be distressed. Midazolam is the agent most studied, and has an excellent safety profile. An oral dose of 0.5-0.6 mg/kg or intranasal dose of 0.2 mg/kg seems effective. Most children have not had a VCUG previously, and it may be difficult to predict which of them will go on to have distress. When giving oral midazolam of 0.5 mg/kg to children routinely, the number needed to treat them is 2.9 (95%CI 1.9–5.5) to eliminate serious or severe distress. Continuous flow nitrous oxide appears promising, particularly with a fast onset and recovery time, but it has greater potential for deeper sedation. This may interfere with voiding, and further studies are required. Midazolam appears not to interfere with the VCUG's ability to diagnose vesicoureteric reflux using indirect (residual volume) and direct (VUR grading) measures. There are many children who would avoid distress if they were given sedation. Local sedation services should be engaged, and safety guidelines should be followed to ensure that this effective treatment might be implemented safely.

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Review Article

The PIC Cystogram: Its Place in the Treatment Algorithm of Recurrent Febrile UTIs

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Purpose. A common pediatric dilemma involves management of children with recurrent febrile urinary tract infections (UTIs) who have normal voiding cystourethrograms. Vesicoureteral reflux (VUR) has been demonstrated in such cases by performing a cystogram which positions the instillation of contrast (PIC) at the ureteral orifice. We describe the evidence supporting this diagnostic test. *Materials and Methods.* The literature was searched to identify and subsequently evaluate all studies investigating PIC cystography. *Results.* In patients with febrile UTIs and negative VCUGs, the PIC cystogram has been demonstrated to identify occult reflux (PIC-VUR). When identified and treated, these patients have a significant reduction in the incidence of febrile UTIs. *Conclusions.* Although the current literature on PIC cystography is limited, it appears to be a clinically useful test in a select group of patients with recurrent febrile UTIs, that are not found to have VUR on a conventional VCUG. A prospective randomized trial is underway to further define its role in the treatment algorithm of febrile UTIs.

1. INTRODUCTION

UTIs result in over 1 million physician visits annually, affecting from 2.4% to 2.8% of children. Reference [1] Many of these patients will go on to have recurrent infections. Reference [1] Recurrent febrile UTIs, while not a proven risk for renal damage, contribute to economic burdens for the family and society because of the recurrent medical needs and hospitalizations. Inpatient hospital costs alone are estimated to be greater than 180 million dollars per year [1]. These figures do not consider the societal impact of such UTIs on days children lose from school or parents miss work.

Less than 50% of patients with febrile UTIs demonstrate VUR. Despite an adequate work up to include characterization of the type and source of bacteria, upper tract evaluation to include renal ultrasound and DMSA renogram, and lower tract evaluation to include voiding cystography and diagnosis of dysfunctional elimination syndrome (DES), the etiology of recurrent febrile UTIs often remains elusive. The empiric management of these patients often involves administering antimicrobials intermittently when infections occur or chronically as prophylaxis.

Because we have been dissatisfied with such empiric management, we have pursued further testing for reflux in such patients with recurrent febrile UTIs who show no evidence of reflux on a conventional VCUG. This testing is known as the positioned instillation of contrast (PIC) cystogram. This is done during cystoscopy by positioning the instillation of contrast at the ureteral orifice under fluoroscopic control. This is a test to check for VUR that may be clinically significant yet was not identified on the conventional VCUG. The historical evolution of this test was based upon observations that many of these children were found to have patulous orifices that easily distended with the flow of water (i.e., hydrodistention) when they were evaluated endoscopically. Noted hydrodistention was then followed by checking for VUR using radiographic contrast fluid. As the reflux was demonstrated on PIC, but not by conventional VCUG, it is termed occult. We detail the current knowledge regarding the test and our view on its

place in the current management scheme of children with recurrent febrile UTIs who do not have VUR on conventional VCUG.

2. PIC CYSTOGRAPHY TECHNIQUE

PIC cystography is performed at the time of cystoscopy. After induction of general anesthesia, the child is placed in the dorsal lithotomy position. Using a rigid cystoscope, the urethra and bladder are systemically evaluated for anatomical abnormalities such as ureteroceles, diverticuli, and mucosal abnormalities. The ureteral orifices are identified and evaluated for their position and trigonal appearance. The ureteral orifices are then evaluated for insufficiency, VUR, as follows:

(i) the bladder is emptied,

(ii) the cystoscope beak is positioned facing the ureteral orifice, close enough to the ureteral orifice so that the orifice fills the cystoscopic view but not inside the orifice,

(iii) contrast to be instilled is placed at a height of 1 meter above the level of the bladder. This is the height of contrast flow done for a conventional VCUG,

(iv) via the irrigation port of the cystoscope, contrast is flowed toward the ureteral orifice while fluoroscopy is done,

(v) the bladder is then emptied and the procedure is repeated on the contralateral side [2].

If the ureteral orifice is insufficient to prevent reflux of contrast, hydrodistention will be noted at cystoscopy and VUR will be imaged by fluoroscopy.

3. PILOT STUDIES ON PIC CYSTOGRAPHY

In 2003, Rubenstein et al. introduced the technique and their experience in using this test. Fifty seven children who underwent cystoscopy were evaluated. The data was analyzed by comparing the results in a control group versus those in the study group. The control group was comprised of 2 sets of patients: (a) patients not expected to demonstrate VUR as there was not a history of febrile UTI, the ultrasound was normal, and the conventional VCUG was normal (15 patients, 30 ureteral orifices) and (b) patients expected to demonstrate VUR on a PIC cystogram as there was a history of febrile UTI and VUR was seen on conventional VCUG (12 patients, 24 ureteral orifices). The study group was comprised of patients with recurrent febrile UTIs, a normal ultrasound, and a normal VCUG (30 patients, 60 orifices) [2]. The analysis of data for the control group (a) in which all patients were not expected to demonstrate VUR demonstrated that all orifices appeared normal and none demonstrated PIC-VUR. In the analysis of data for the control group (b) in which all patients had VUR on conventional VCUG, all 15 ureteral orifices with known VUR showed lateral ectopia and/or patulous morphology, and hydrodistention and also demonstrated PIC-VUR. A total of four ureteral orifices appeared normal and did not exhibit VUR by VCUG or PIC cystography, and 5 were lateral and/or patulous and did not demonstrate VUR by VCUG but did show PIC-VUR. From this data, Rubenstein concluded that PIC cystography was 100% sensitive and 91% specific in identifying VUR [2]. These findings in the control group are very important since this demonstrates that a patient with a normal orifice will not artifactually reflux with PIC cystography.

In the study group, all 30 patients had at least one orifice with abnormal morphology. PIC-VUR was identified in all these patients with a history of febrile UTIs. All were treated for VUR with either antimicrobial prophylaxis or reimplantation. During 8-month followup, no patients experienced a recurrent febrile UTI [2].

More recently, Tareen et al. performed a similar study in a small number of patients resulting in their recommendation that the PIC cystogram should be part of the algorithm in evaluating patients with recurrent febrile UTIs without VUR on VCUG. All 5 patients in this study with radiographic confirmation of pyelonephritis showed PIC-VUR. All were treated with endoscopic injection of dextranomer/hyaluronic acid copolymer or vesicoureteral reimplantation. In a followup from 11 to 16 months, no patient has had recurrence of febrile UTIs [3].

From these initial reports, it is concluded that occult VUR identified by PIC cystography may provide an explanation for recurrent febrile UTIs in patients with otherwise negative radiographic studies.

4. MULTI-INSTITUTIONAL EVALUATION OF PIC CYSTOGRAPHY

These initial experiences with treatment of VUR demonstrated by PIC cystography for febrile UTIs sparked the establishment of a multi-institutional registration of cases by Edmondson et al. [4]. Four centers performed PIC cystography on 39 consecutive patients with febrile UTIs and negative VCUGs. PIC-VUR was identified in 82% of the patients with febrile UTIs and negative VCUGs. A strong correlation between the ureteral orifice appearance, hydrodistention and the presence of VUR was identified. If the orifice was patulous, it was 38 times more likely to demonstrate VUR. Laterally displaced orifices were 9 times more likely to demonstrate VUR. Also 100% of orifices that hydrodistended were positive for VUR [4].

This multi-institutional registry demonstrated a similar and reproducible incidence of PIC-VUR in patients with recurrent febrile UTIs as Rubenstein's inaugural study. The study also further established a correlation between orifice location and morphology.

5. CLINICAL IMPORTANCE OF PIC CYSTOGRAPHY

To further examine whether PIC-VUR is simply a radiographic observation or an entity with clinical relevance, the following studies were performed.

Hagerty and the PIC Cystography Group concluded that PIC-VUR is clinically significant by determining that the

incidence rate of febrile UTI is lowered significantly by treatment of VUR identified by PIC. 14 centers enrolled 118 patients with recurrent febrile UTIs, who demonstrated PIC-VUR. Patients were treated with underwent endoscopic injection (104), ureteral reimplantation (3), or antimicrobial prophylaxis (11). Overall, the incidence rate for febrile UTI decreased significantly from 0.16 per case/mo before PIC-VUR treatment to 0.008 per case/mo after treatment. The post treatment rate of febrile UTI in cases treated with antibiotic versus surgery was not significantly different [5].

Noe and Williams also described their experience with PIC cystography and simultaneous dextranomer/hyaluronic acid copolymer injection in 47 children with a history of pyelonephritis and negative VCUG. Success was defined as no further febrile UTIs. Repeated VCUGs were not performed as in the prior studies, as they were negative prior to treatment. A total of 75% of the patients had PIC-VUR and were treated endoscopically with dextranomer/hyaluronic acid copolymer. Three of the patients developed febrile UTIs after surgery and underwent ureteral reimplantation. None of these patients have had recurrent febrile UTIs. Only one patient has had an afebrile UTI during followup. Of the 12 patients who did not have PIC-VUR, each only had 1 febrile UTI, not recurrent UTIs, prior to cystoscopy [5].

Both of these studies further demonstrate that when a patient with febrile UTIs, with no other clear diagnosis, is identified as having PIC-VUR and is treated, they do not have recurrent febrile UTIs. This reinforces the concept that occult reflux identified by PIC cystography in patients with febrile UTIs is clinically significant and that the PIC cystogram is an important testing modality that should be included in the present algorithm of the evaluation of patients with recurrent febrile UTIs.

6. THE REPLACEMENT OF POSTOPERATIVE VCUC WITH PIC CYSTOGRAPHY

Pinto et al. researched the feasibility of avoiding the need to perform a VCUG on an awake child after reflux treatment by performing a PIC cystogram immediately after endoscopic injection. Pinto found the PIC cystogram was not useful for this purpose in a study involving 61 patients with VUR identified on VCUG. Patients underwent dextranomer/hyaluronic acid copolymer injection followed by PIC cystography. If the PIC cystogram was positive, no further injection of dextranomer/hyaluronic acid copolymer was given. The results of the PIC cystogram were compared to the VCUG done at 3 months postoperatively. Three ureters had positive PIC cystograms. None of these patients were found to have VUR on postoperative VCUG. Also, 14 patients had persistent VUR on VCUG despite a negative PIC cystogram at the time of injection [6]. In addition, Palmer has also demonstrated no correlation between intraoperative cystography and postoperative conventional cystography [7]. Our anecdotal experience with this method shows similar results.

Currently, there is no evidence to support the use of PIC cystography after endoscopic injection to predict postoperative outcomes. Therefore, it is not recommended to replace a postoperative VCUG with a PIC cystogram at the time of endoscopic correction of VUR.

7. PHYSICS OF PIC CYSTOGRAPHY

The impact of intravesical pressure upon the status of PIC-VUR was examined from historical clinical considerations, in vitro simulation study, and clinical examination. Historically, it is commonly held that VUR may be induced in a normal ureteral orifice by conditions which chronically impose supraphysiological pressure such as neuropathic or nonneurogenic neurogenic bladder; however it is commonly held that VUR is not able to be induced by acute application of elevated intravesical pressure [2]. We have demonstrated that when the PIC cystogram is performed as described above the intravesical pressure local to the ureteral orifice pressure is physiological (<20 cm water). In contrast, the practice of hand injection of contrast is associated with a supraphysiological pressure (>100 cm water) [8].

8. CLINICAL USE AND FURTHER DIRECTIONS

Currently, there are several widely accepted explanations for recurrent UTIs including the presence of various host and bacterial virulence factors, as well as inadequately treated DES. Nevertheless, it is becoming widely accepted that it is also possible that this type of patient may have occult reflux, not identified on conventional VCUG, that can allow ascent of a lower tract infection to an upper tract infection that is febrile in nature. If so, identification and treatment of this form of occult reflux, PIC-VUR, results in a decrease in recurrent febrile UTIs. The PIC cystogram represents a relatively simple objective way to identify this type of occult VUR that may be clinically significant.

In a recent debate on PIC cystography at the Society of Pediatric Urology it was argued that there is little data evaluating whether or not occult VUR identified by PIC cystography can cause renal injury. In addition, febrile UTIs as described in most of this research on PIC cystography, do not necessarily equate pyelonephritis [9]. While these observations are valid, it is important to note that while it is unknown whether or not occult reflux identified with PIC cystography results in renal scarring, the present evidence clearly demonstrates that treatment of this occult reflux with either prophylactic antibiotics or surgery decreases the rate of recurrent febrile UTIs and its associated morbidity. Even though many of these patients may not have significant renal scarring or be at risk for renal damage, the clinical benefit to these patients is extremely important. However, it will be important to evaluate these important issues as they relate to renal scarring in future studies. In the end, the ability to identify a causative factor that can be treated and reduce or eliminate future febrile infections and the morbidity associated with them is beneficial to both patients and their families.

To more definitively define the clinical significance of PIC cystography, a prospective randomized trial is now underway in which patients who are identified as having PIC-VUR are being randomized into 2 study groups: observation

(no antibiotics or surgery) and treatment (endoscopic or open surgical correction of reflux) [10].

9. CONCLUSION

Many children with recurrent febrile UTIs do not demonstrate VUR on conventional VCUG. Thus, in such children, there is neither a treatable diagnosis nor an evidence-based treatment plan. This scenario may become associated with significant morbidity such as the need for hospitalization and renal damage. A treatable diagnosis could improve structuring a management strategy. The current research on PIC cystography shows that the PIC cystogram can identify clinically significant occult VUR. When this occult reflux is treated, the incidence of recurrent febrile UTIs is significantly reduced. We conclude that including the performance of PIC cystography in the present algorithm management of patients with recurrent febrile UTIs and normal conventional VCUGs will aid structuring an evidence-based treatment plan. Future prospective randomized studies are currently underway to refine our understanding of the natural history of occult reflux and the role that PIC cystography has in identifying this type of reflux.

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Review Article

Radiation Safety and Future Innovative Diagnostic Modalities

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One must demand an accurate, safe, radiation-free, and noninvasive method for reflux examination as the ideal possibility for reflux screening. Of course the available different imaging modalities are far from this ideal situation, but minimal radiation exposure is indeed a permanent objective. Additionally since all of these studies might be quite stressful to the child and the family, a specially designed and equipped environment is obligatory for the comfort of all involved. An absolute ideal modality in the diagnosis of VUR would be the definition of a certain marker in serum or urine that could identify children with VUR without the need for any interventional screening modality. Therefore more and more efforts have to be made in the future to investigate different markers for this purpose. Since reflux is one of the most frequent congenital conditions pediatric urologist have to deal with potential risks that might lead to renal insufficiency, noninvasive and radiation-free modalities should become the methods of choice, hopefully in the near future.

1. INTRODUCTION

Different imaging modalities for evaluating vesicoureteral reflux (VUR) are nowadays available and more and more attention is paid to concerns about radiation safety, especially when multiple imaging studies are necessary with repeat exposition to ionizing radiation during a conservative follow up. Minimal radiation exposure is now a permanent objective.

Experience and logistic availability are often responsible for choosing the one or the other imaging study. Moreover, patient age, gender, race, and parental preference and anxiety about invasiveness and radiation exposure play an additional role as well.

In the past years, different innovative techniques like low-dose fluoroscopy have definitively decreased radiation dose to the patient. On the other hand, diagnostic quality images are mandatory for appropriate diagnosis and treatment. Ultrasonography, nuclear medicine, and magnetic resonance are preferred to intravenous urography and computed tomography whenever possible. In general, voiding cystourethrography has frequent indications in pediatric urology and efforts are made to replace it by radionuclide cystograms or sonocystograms in order to reduce the exposure to ionizing radiation.

Furthermore, there is also no consensus about the timing of evaluation for possible reflux as well as in the conservative follow up or after intervention.

2. VOIDING CYSTOURETHROGRAPY, RADIONUCLIDE CYSTOGRAPHY, SONOCYSTOGRAPHY

All these three modalities can be used to demonstrate the presence or absence of VUR. Voiding cystourethrography (VCUG) as well as direct radionuclide cystography (RNC) are invasive diagnostic tools with the need for patient preparation and catheterization and the exposition of the patient to ionizing radiation although VCUG is a fluoroscopic examination and RNC a nuclear medicine study, respectively. Additionally, an indirect RNC with the intravenous administration of technetium-99m-labeled diehtylenetriamine pentaacetic acid is a possible tool with the assumption of a possible VUR when radioisotope counts increase in the renal areas after voiding. But the false negative rates may vary between 22 to 51% [1].

Even though being invasive as well since catheterization is mandatory, the big advantage of performing a sonocystography is the prevention of any ionizing radiation to the patient at all.

For a conventional VCUG, a water soluble contrast medium is instilled into the bladder after preparation and transurethral sterile catheterization. An option is the suprapubic administration of the contrast, but still invasive. Different fluoroscopic images are taken to demonstrate the presence or absence of vesicoureteral reflux.

The same procedure (preparation and catheterization) is necessary for performing an RNC. Usually technetium 99m pertechnetate is the radiopharmacon of choice to be instilled into the bladder. The radioactive emissions are continuously recorded with a gamma camera.

When comparing these two wide spread diagnostic modalities, the big advantages of a classical VCUG are the provision of high-resolution images with a clear evaluation of the bladder wall, the urethra especially in males [2], any sign of intrarenal reflux as well as a clear grading possibility. It is also supplementary reliable for detecting duplication, ureteral ectopia with or without ureteroceles, and posterior urethral valves. That is why especially in boys and also for the initial investigation in girls a classical VCUG is still the preferred method of choice by many investigators. On the other hand, the expense is a much higher dose of ionizing radiation to the patient.

Although recent improvements introducing low-dose fluoroscopy techniques and pulse fluoroscopy with the add of digital enhancing modalities have decreased the radiation dose to the patients dramatically [3–5], still a VCUG exposes the patient to almost 100 times the radiation of an RNC. A special concern is the quite high gonadal radiation dose particularly with multiple studies of fluoroscopic monitoring [6]. Of course gonadal shielding in males and careful imaging coning help to decrease the patient's radiation exposure. Moreover, with the use of a low-dose fluoroscopic system in conjunction with a computer-based video frame grabber, the ovarian radiation dose may become comparable to RNC [3]. A VCUG performed with an optimized pulsed fluoroscope can achieve "as low as reasonably achievable" (ALARA) levels and of course maintain diagnostic image quality. With such a setting radiation dosage can be reduced to 10% that of continuous fluoroscopy thus resulting in dosages at about 10 times that of RNC. Therefore, pulsed fluoroscopy is currently the recommended standard [7, 8].

On the other hand, a direct RNC allows continuous monitoring for VUR throughout the whole examination time without any additional radiation introduced. Therefore, some authors prefer RNC to be more sensitive in the diagnosis of VUR [9] although precise grading is impossible. But this makes it probably an ideal methodology for the conservative follow up and after any antireflux intervention.

The main advantage of RNC over fluoroscopic VCUG is definitively decreased radiation exposure of the patient. The average effective radiation dose of a VCUG using low-dose fluoroscopy is around 3 mrem, compared to 0.5 mrem for an RNC. Of course the average effective dose of the VCUG is variable and depends on the patient size, operator, and machinery [8]. The sensitivity of RNC for detecting reflux is equal to or even greater than that of VCUG; however, the spatial resolution and anatomic detail seen on an RNC are ultimately inferior to those seen on a VCUG [10].

Sonocystography may be used as a very sensitive tool in the detection of a possible VUR especially since the intervention of various ultrasound echo enhancing agents [11]. First, attempts with this technology have been made back in 1976. The capability of echo-enhanced refluxsonography extends further in that the method may enable complete eliminationof any radiation exposure. This may justify the longer examination time compared with that of VCUG. Using an X-ray contrast agent, a certain concentration at a given time is necessary to be able to see the contrast, whereas even single microbubbles can be visualized with the ultrasound method. This together with the duration of the ultrasound examination as well might be responsible for the detection of some low grade refluxes that might be missed using VCUG and RNC. Moreover, this method allows for cyclic fillings without any additional radiation as well. On the other hand, similar to RNC, the lack of diagnostic visualization of anatomic details and particularly the urethra represent a disadvantage of the ultrasound methodology. Additionally, the interobserver variability might be quite high and a specially trained examiner is obligatory. In summary, of the available literature on that issue, the comparative aggregated data between sonocystography and VCUG indicate that reflux exclusion and diagnosis between the two methods is highly concordant and that the discordant findings are primarily due to more reflux episodes being detected solely by sonocystography and that these reflux episodes are of higher grade and consequently may be clinically more relevant than the predominantely low grade reflux found only on VCUG and that finally the high negative predictive value of sonocystography may have practical consequences as it demonstrates that sonocystography may be suitable for screening purposes [12, 13].

3. CONCLUSION AND FUTURE MODALITIES

One must demand an accurate, safe, radiation-free, and noninvasive method for reflux examination as the ideal possibility for reflux screening. Additionally, since all of these studies might be quite stressful to the child and the family a specially designed and equipped environment is obligatory for the comfort of all involved. Preparation and education of the families help to reduce discomfort. If needed, sedation with the use of midazolam can be beneficial without any negative influence on the outcome of the examination [14].

Contrast enhanced ultrasound allows an accurate and safe diagnosis and is in addition to VCUG and RNC radiation free as well; but unfortunately, still an invasive procedure with the insertion of a catheter. A future prospective might be an exogenous bubble generation to fulfil one of the most important criteria in reflux diagnosis: being noninvasive. Efforts are already being made to achieve this goal. Till then nuclear medicine studies and contrast studies will remain essential for the evaluation of VUR.

An absolute ideal modality in the diagnosis of VUR would be the definition of a certain marker in serum or urine that could identify children with VUR. Basic research is going on to investigate different markers that have been found to be elevated in children with VUR [15]. Measured levels

of microproteinuria, urine retinol-binding protein, urinary prostaglandine E_2, urinary β_2-microglobulin, urinary interleukin levels, and serum endothelium leukocyte adhesion molecule have been shown to be elevated in patients with VUR compared to controls. So far, none of these methods can localize which kidney is affected by reflux nor can they assess the grade but they probably offer the potential advantage of rapidly screening for VUR.

Another marker, β-hexosaminidase, has been shown to be higher in patients with VUR and renal scarring [16]. Tamm-Horsefall protein (THP) is another high-molecular-weight glycoprotein that is exclusively present in the kidney and not secreted elsewhere. In children with intrarenal reflux, it is also detectable in blood vessels and lymph nodes. It is believed to accumulate from leakage of adjacent ruptured tubules [17]. Interestingly, in a study on children with surgically corrected VUR but no improvement on renal function postoperatively, THP levels remained elevated before and after surgery [18]. Still a lot of research has to be undertaken to minimize or hopefully abandon the burden of one of the widest used imaging modalities in pediatric urology.

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Review Article

Antibiotic Prophylaxis in the Management of Vesicoureteral Reflux

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Antibiotic prophylaxis has been, since 1960s, one of the management options in treating vesicoureteral reflux. The purpose of this review article is to provide a concise overview of the rational for antiobiotic prophylaxis and to discuss the various agents used. Some of the current controversies regarding use of antibiotics for reflux will also be presented.

1. INTRODUCTION

Once vesicoureteral reflux (VUR) has been diagnosed, the basic premise in management is to prevent further ascending urinary tract infections (UTI) which may, if left untreated, lead to pyelonephritis. Pyelonephritis, in turn, would lead to potential renal damage [1]. Based on the work of Jean Smellie et al. in 1960s, use of antibiotic prophylaxis was found to be helpful in reducing the recurrence rate of urinary tract infection in children with VUR [2]. Subsequently, several long-term studies have demonstrated the validity of the concept [3–7]. The basis for the antibiotic prophylaxis in patients with VUR was the fact that, ultimately, reflux in low grades (I through III) was recognized to resolve over time and thus maintenance on low-dose antibiotic would prevent or reduce the risk of urinary tract infection until such time that the reflux would disappear [8]. The goal of this article is, therefore, to review the management of VUR using antibiotic prophylaxis, its advantages and disadvantages based on a review of the literature. The various antibiotic used for prophylaxis in VUR will be discussed.

2. THE EVOLUTION OF ANTIBIOTIC PROPHYLAXIS IN THE MANAGEMENT OF PATIENTS WITH VUR

Regurgitation of urine from the bladder up into the ureter and renal collecting system has been recognized since early times [9]. VUR became identified as an etiologic factor for pyelonephritis from the classic studies carried out by Hutch, who in 1952, studied a group of paraplegic patients diagnosed with neurogenic dysfunction of the bladder and VUR. Reflux of infected urine into the upper urinary tract was postulated to be the cause of chronic and progressive renal damage [10]. Later, in 1959, Hodson observed that reflux seemed to be more common in children with urinary tract infections and that there was a correlation between reflux and chronic pyelonephritis as documented by VCUG (voiding cystourethrogram) and IVU (intravenous urogram) [11]. As the association between VUR and urinary tract infection became more established, additional experimental studies demonstrated the role of bacterial infection in causing renal damage in patients found to have VUR [12–14].

Historically, the initial approach to treating patients with reflux was observational without continuous antibiotic. Treatment was offered only as infections occurred. Unfortunately this approach demonstrated that renal damage could occur in patients who had had only one infection and that further renal damage was more likely to occur in kidneys that were noted to have parenchymal lesions but could also occur in normal kidneys. Lenaghan reported that most infections occurred within the first five years after the initial diagnosis [15]. In light of the high rate of new kidney damage noted in children treated with intermittent antibiotic therapy, it was suggested that prophylactic antibiotic be used. Lenaghan's conclusions were confirmed by the international reflux study

in children which also demonstrated a high rate of new scar formation in children who were observed off continuous antibiotic prophylaxis but with known reflux [16]. This study found that new renal damage occurred in 12.5% of children with normal kidneys, whereas 62% of scarred kidneys showed progression of the damage as infections were treated. A number of subsequent studies showed that progression of scarring in patients with reflux could occur in the face of recurrent urinary tract infection [17, 18]. N. P. Goldraich and I. H. Goldraich, in 1992, showed that, in a large prospective study children with VUR of grades I through V treated with antibiotic prophylaxis, a relatively low rate of new scar formation (3%) was found and this was seen only in cases where urinary tract infection occurred [19]. The Southwest Pediatric Nephrology Study Group demonstrated that in a relatively small group of patients with grade 1–3 reflux followed for five years, 12 patients (10.7%) developed new scars on Intravenous Urogram intravenous urogram (IVU) in the face of breakthrough infections [20]. Skoog et al. observed a large cohort of patients (545) on continuous low-dose antibiotic prophylactic for up to ten years. A relatively low rate of progressive scarring in the kidneys was noted (0.5%) mostly occurring in children with breakthrough infection [21]. Current recommendations for antibiotic prophylaxis in children have been formalized by the AUA guideline panel on the management of primary VUR in children [22]. Recommendations from the guidelines were that children with VUR grade I through IV could be initially managed medically with continuous antibiotic prophylaxis because of fewer risks, in the short term, and that surgery would be recommended for children who experienced breakthrough infections.

More recently the concept of stopping antibiotic prophylaxis after a certain age has been evaluated as parents have increasingly become weary of long-term medication intake and concerns have been raised about side effects and bacterial resistance. Based on the findings that, by age 4, renal scarring was unlikely to occur in the face of urinary tract infection, cessation of antibiotic prophylaxis was felt to be reasonable in children beyond the age of 5 [23, 24]. Cooper et al. evaluated a group of 51 patients with reflux with a mean age of 8.6 years who were not treated with prophylactic antibiotic [25]. Despite the fact that reflux persisted in the majority of these patients, only a small number of patients (11%) developed a subsequent urinary tract infection. No new renal scars were noted as documented by ultrasound, which, however, may not be the most accurate modality to ascertain for renal lesions. Unfortunately, no long-term double blinded randomized study has been carried out to compare the efficacy of antibiotic prophylaxis versus no antibiotic prophylaxis in patients diagnosed with VUR based on the degree of reflux. In addition, the data is still not entirely clear with regard to the comparison between surgical therapy and antibiotic prophylaxis. The International Reflux Study in Children (IRSC) failed to demonstrate a clear advantage of any of these two forms of management [26]. The major limitations of the study were that not all grades of reflux were managed by either modality, since higher grades of VUR were treated surgically thus introducing a serious selection bias. Currently, medical management of VUR still remains commonly practiced for younger patients with lower grades of VUR as the randomized studies are being set up.

3. ANTIBIOTICS USED FOR PROPHYLACTIC TREATMENT IN PATIENTS WITH VUR

A relatively small number of antimicrobials are used to treat urologic conditions in children, the most common ones being used for antibiotic prophylaxis in the face of VUR are trimethoprim-sulphamethoxasole (TMP/SMX), nitrofurantoin, and penicillin derivatives amoxicillin. The advantage of these antibiotics is that their active form or metabolites are excreted in the urine thus keeping the urine free of bacteria. Guidelines for administrations will not be reviewed but it should be kept in mind that only penicillin derivatives are used in younger children under 2 months of age because the immaturity of the newborn liver and kidneys results in a slower metabolism and excretion of these medications [27]. Allergic reactions to antimicrobials should always be a concern. A family history is helpful in determining which child may actually be allergic to a medication. Allergic reactions manifest themselves as either urticaria, diffuse skin rash, or, more rarely, anaphylaxis. Subcutaneous skin testing may resolve the question of an allergic reaction to medication but since the testing itself may be associated with some risk of allergic reaction this should be performed under controlled conditions by an allergist. A 5% cross allergenicity between penicillin and cephalosporin should also be recognized [28]. In general, however, children who have mild or delayed allergic reaction to one of these classes of antimicrobials are usually able to tolerate agents in other classes.

Bacterial drug resistance is a growing problem worldwide. In 1980s, widespread recognition of the issue came about with the widely reported vancomycin resistant staphylococcal aureus infection found in cases of community acquired infection [29]. The incidence of drug resistance has clearly increased over the last 20 years and has become a major health issue. Control of antimicrobial resistance is clearly a multifaceted task involving hospital policy, individual provider practice, and patient compliance. Guidelines that have been developed by the Joint Committee on Antimicrobial Resistance to help decrease the emergence of drug resistance organism include a careful use of broad spectrum antibiotic, the tailoring of therapy to sensitivity profiles, and the avoidance of unnecessary prolonged therapy [30].

We will review the specific antimicrobials used in patients with VUR for prophylaxis of infections. These include penicillins, TMP-SMX, and nitrofurantoin.

The penicillin class of antimicrobials includes natural penicillins (V and K), amino penicillins (ampicillin and amoxicillin), the beta-lactamase resistant penicillins (methicilin, nafcilin, oxacillin, dicloxacillin), and the antipseudomonal penicillins (carbenicillin, ticarcillin, azlocilin, and mezlocillin). The natural penicillins are used to prevent and treat infections caused by group A streptococci and S pneumonia. These medications are now rarely used for

prophylaxis because of their limited commercial availability and because resistance patterns have increased. Amino penicillins have become the most commonly used penicillins. They are the drug of choice in treating enterococcal urinary tract infection and can be used for prophylaxis in infants under age 2 months. These agents are usually effective against most bacteria susceptible to Penicillin G as well as some Penicillin G resistant gram negative bacilli [31]. Amino penicillins are excreted primarily by the kidney. Ampicillin is available both in oral and intravenous formulation but Amoxicillin is only available as an oral agent. Amoxicillin has better bioavailability than ampicillin because more of it is absorbed from the digestive tract. A higher percentage of unabsorbed oral ampicillin remaining in the gut alters gut flora frequently leading to GI upset and diarrhea which may be a concern in younger children. A higher rate yeast infections has also been noted. Beta-lactamase-resistant penicillins are usually not used for prophylaxis as are the antipseudomonal penicillins. Reactions to penicillins are relatively rare and include hypersensitive reactions, neurotoxicity, nephrotoxicity, and hematologic toxicity [32].

Trimethoprim/sulfamethoxazole is a combination agent that inhibits the production of bacterial folic acid, thereby blocking DNA synthesis. It is the most widely used outpatient antibiotic agent used for prophylaxis in children with vesicoureteral reflux. While trimethoprim (Primsol) alone has a similar antibacterial activity to sulfamethoxazole, the spectrum of activity expands when the drugs are combined. In addition, resistance develops less quickly in the combined formulation than with either drug alone [33]. Sulfamethoxazole and trimethoprim are both absorbed rapidly after all administration. The majority of sulfamethoxazole undergoes hepatic metabolism to inactive metabolites, while approximately half of the absorbed trimethoprim is converted hepatically into inactive metabolites. Most of the active and inactive drug is then excreted by the kidney into the urine [34].

The adverse reactions associated with this combination of drug are most often caused by the sulfa component. These reactions include hypersensitivity reaction (ranging from a mild rash to severe Stevens-Johnson exfoliative reaction which may be severe and life threatening), severe photosensitivity reaction, and hematologic toxicity that presents as agranulocytosis or hemolytic anemia, prompting the recommendation that a complete blood count be obtained in children who are taking sulfa medications for extended periods of time. Sulfonamides are contraindicated in children younger than 2 months of age because the sulfa moiety from the drug can displace bilirubin from its natural albumin binding site, predisposing infants to hyperbilirubinemia [35].

Nitrofurantoin is an agent widely used for the prophylactic management of VUR. While it is most commonly administered in an oral formulation, a parenteral form is also available. It is well absorbed orally and undergoes significant hepatic degradation to inactive metabolites. Because of its extended metabolism and relatively poor tissue penetration, nitrofurantoin is used solely as a urinary tract desinfectant since it will achieve bacteriocidal concentration only in urine. [33]. Although its exact mechanism of action is unknown, nitrofurantoin is thought to inhibit bacterial acetyl coenzyme A, thereby interfering with carbohydrate metabolism. It may also disrupt bacterial cell wall synthesis. Nitrofurantoin is usually effective in treating staphylococci, streptococci and most community acquired gram negative uropathogens. Despite its widespread use, bacteria rarely develop resistance to nitrofurantoin. This is most probably due to the fact that the drug does not achieve significant levels in intestinal or vaginal tissues and does not alter the normal flora in these areas [36]. The most common side effect associated with nitrofurantoin is GI upset with nausea, vomiting, or diarrhea. Use of the microcrystalline formula and administration with meals usually eliminates these side effects. A rare, more severe side effect is pulmonary fibrosis, which is most likely to occur after long-term therapy (months to years) and can present acutely with episodic coughing and/or dyspnea which would warrant a full evaluation. Hemolytic anemia can occur in patients with glucose-six-phosphate dehydrogenase deficiency as well as in infants under one month of age.

Cephalosporins are rarely used for antibiotic prophylaxis unless patients have shown resistance to TMP/SMX. Because of their broad activity against community acquired pathogen, this class of antimicrobial is usually used for surgical prophylaxis or for acute treatment of urinary tract infection. Cephalosporins provide a reasonable antimicrobial activity against most gram positive and gram negative bacteria. Use of prophylaxis is usually not recommended as the medications tend to be expensive. However, some cephalosporins including Cephalexin have prolonged urinary concentration and may be helpful for short-term antibiotic prophylaxis.

Fluoroquinolones inhibit action of the essential bacterial enzyme DNA gyrase which consequently prohibits maintenance of the superhelical twist in the double stranded DNA causing rapid cell death [37]. One important clinical aspect of the antibacterial spectrum of fluoroquinolones is their effectiveness in treating hospital acquired organisms. These antimicrobials have good pharmacokinetic qualities which include rapid absorption from the intestinal tract, good tissue penetration, and good intracellular diffusion. Long-term use of fluoroquinolones in a pediatric population has been reported to be effective and safe in patients with cystic fibrosis [38]. Ciprofloxacin in children seems to be well tolerated with no significant evidence of arthropathy, bone abnormalities, and no serious adverse side effects [39]. However, fluoroquinolones have not become an acceptable form of antibiotic prophylaxis given their expense and given the risk for possible emergence of resistant organism to this class of antimicrobials [40].

4. THE DOWN SIDES OF ANTIBIOTIC PROPHYLAXIS IN THE MANAGEMENT OF VUR

Three interrelated issues come into play when considering prophylactic antibiotic therapy for VUR: compliance, efficacy, and long-term side-effects of chronic antibiotic administration. Let us examine each of these issues. A recent

report indicate that long-term administration of a daily antibiotic may not be carried out as carefully and consistently as one would hope. Hensle et al. in a review of patterns of care based on health insurance data showed that only 17% of patients were at least 80% compliant with prophylactic treatment [41]. In addition, as time goes by, compliance with antibiotic intake has been shown to go down by the first year follow-up visit [42]. Efficacy of antibiotic therapy in reducing the rate of urinary tract infection is hard to evaluate as no long-term, randomized placebo-controlled studies have, to date, been published. The Cochran Database Systematic Review meta-analysis reported that there was no significant difference in risk for urinary tract infection between daily antibiotic prophylaxis and no prophylaxis or between intermittent (3 days per week) prophylaxis and no prophylaxis [43]. The report also found no difference in the risk of renal parenchymal damage between the various treatment options. In addition the review indicated that 30 to 50% of patients on antibiotic prophylaxis were reported to have a UTI within 5 years. In a recent multicenter, randomized study of antibiotic prophylaxis treatment of patients with lower grades of VUR, Garin et al. showed a similar one year urinary infection rate between patients who were treated with or without antibiotic prophylaxis: 23.6% of children with grade 1 through 3 reflux received antibiotics and acquired a urinary tract infection while 22.4% of those on no antibiotic prophylaxis acquired one. Interestingly, those patients on antibiotic prophylaxis were found to have a higher rate of pyelonephritis upon follow-up [44]. Recurrent infections are, therefore, a worrisome issue in patients with VUR maintained on antibiotic prophylaxis. Sjöström reported a rate of breakthrough urinary tract infections in patients with reflux up to 47% of case [45]. Whether or not these infections are harmful in the long term is unclear but this persistent ability to acquire urinary tract infection clearly brings into question the efficacy of antibiotic prophylaxis and the role of host susceptibility to infections. If one looks at the ability of prophylactic antibiotic to reduce the risk for renal scarring, Reddy et al. reported no difference in occurrence of renal damage amongst patients with VUR randomized to receive either antibiotic prophylaxis or no antibiotics [46]. Finally, it would appear that outcomes seem to be rather similar in patients randomly assigned to medical or surgical management [47]. In a recent open-label, randomized study from Italy, antibiotic prophylaxis was not found to be effective in reducing the rate of pelonephritis recurrence and the incidence of renal damage in young children with VUR grades II, III, IV [48].

5. CONCLUSION

Antibiotic prophylaxis still seems to be a reasonable management option after initial diagnosis of VUR especially in children under age five who may be more susceptible to renal damage if an ascending urinary tract infection occurs. Issues of noncompliance, questionable efficacy, potential side effects and allergic reactions, and antimicrobial resistance have now brought into question use of antibiotic prophylaxis in the management of VUR. Further, uncertainty is built into the fact that prediction of reflux resolution varies from patient to patient and may involve other factors than anatomic ones. The complex nature of the interaction between VUR and UTIs and their effects on the kidneys make the identification of those patients at risk for ascending urinary tract infection and subsequent renal damage the biggest challenge in managing VUR. Since the available data is still not sufficient in providing objective guidelines for use of antibiotic prophylaxis in managing VUR, further long-term, randomized placebo-controlled studies are clearly needed to allow better insight into this form of management. In the first year after diagnosis, consistent, low-dose administration of antibiotics may be helpful in reducing the rate of urinary tract infection provided that the right antibiotic is administered keeping in mind the caveat of such a treatment, mainly the rising rate of antimicrobial resistance [48]. It should be noted that cranberry juice may have a role in reducing the rate of UTIs [49]. Parents of children diagnosed with VUR should be apprised of the potential side effects of the medications used for prophylaxis of UTIs and of the other options available for treatment. Reassurance as to the relatively low rate of complication rate seen with antibiotic prophylaxis should be emphasized. Until such studies show unequivocally that antibiotic prophylaxis is ineffective in preventing urinary tract infection and renal damage, antibiotic prophylaxis still remains a viable option in the management of VUR [50].

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Review Article

Antibiotic Prophylaxis for Children with Primary Vesicoureteral Reflux: Where Do We Stand Today?

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The main goal of the management of vesicoureteral reflux (VUR) is prevention of recurrent urinary tract infections (UTIs), and thereby prevention of renal parenchymal damage possibly ensuing from these infections. Long-term antibiotic prophylaxis is common practice in the management of children with VUR, as recommended in 1997 in the guidelines of the American Urological Association. We performed a systematic review to ascertain whether antibiotics can be safely discontinued in children with VUR and whether prophylaxis is effective in the prevention of recurrent UTIs and renal damage in these patients. Several uncontrolled studies indicate that antibiotic prophylaxis can be discontinued in a subset of patients, that is, school-aged children with low-grade VUR, normal voiding patterns, kidneys without hydronephrosis or scars, and normal anatomy of the urogenital system. Furthermore, a few recent randomized controlled trials suggest that antibiotic prophylaxis offers no advantage over intermittent antibiotic therapy of UTIs in terms of prevention of recurrent UTIs or new renal damage.

1. INTRODUCTION

Vesicoureteral reflux (VUR) is defined as the abnormal, retrograde flow of urine from the urinary bladder into the upper urinary tract. VUR can be primary, caused by an anatomically insufficient vesicoureteric junction, or secondary, due to an infravesical obstruction. VUR affects 1–3% of otherwise healthy children. However, the prevalence rises to 10–20% in children with antenatally detected hydronephrosis, to 30% in siblings of children with known VUR, and to 30–40% in children with a proved urinary tract infection (UTI) [1, 2].

The retrograde flow of urine from the bladder into the ureter may transport bacteria to the upper urinary tract, possibly predisposing these children to febrile UTI, which can result in permanent renal parenchymal damage. Ultimately, renal damage results in reflux nephropathy which could cause hypertension and decreased renal function although the risk seems to be lower than previously thought [3–5].

The clinical presentation of patients with VUR is diverse and dependent on age and gender [6]. Typically, VUR is detected during the evaluation of a child, usually a girl, presenting with UTI [7]. Since the widespread use of prenatal ultrasonography, hydronephrosis is often detected in utero, possibly leading to the diagnosis of VUR in the perinatal period [8]. Neonatal VUR is more common in boys and often associated with congenital renal dysplasia. A history of familial VUR and investigation of an overactive bladder can also lead to the diagnosis of VUR [9, 10].

In 1999, the practice guideline from the American Academy of Pediatrics recommended a renal ultrasound and either a classic radiographic voiding cystourethrography or a direct radionuclide cystography after a first UTI in children aged 2–24 months [11]. However, the recently revised guideline of the National Institute for Health and Clinical Excellence (NICE) constitutes a major departure from this diagnostic strategy [12, 13]. For infants and children without recurrent or atypical UTI, no imaging tests are recommended when they are 6 months or older, and an

ultrasound within 6 weeks of the first UTI will suffice when they are younger than 6 months.

Spontaneous resolution of VUR due to the natural elongation of the vesicoureteral junction is possible, especially in patients with the lower grades of VUR or unilateral reflux and in boys; grades I–III reflux resolves at a rate of 13% each year during the first 5 years of follow-up and at 3.5% yearly thereafter, and grade IV reflux resolves at a yearly rate of 5% [14].

The main goal of the management of VUR should be prevention of recurrent febrile UTI, and thereby prevention of the ensuing renal parenchymal damage [6]. The treatment options include intermittent therapy of episodes of UTI, medical therapy with long-term antibiotic prophylaxis, endoscopic therapy, or surgical therapy.

The desire to update our therapeutic algorithm for children with VUR stimulated us to conduct a systematic review of the role of antibiotic prophylaxis in the management of these children. More specifically, we wanted to ascertain whether antibiotics can be safely discontinued and whether prophylaxis is effective in the prevention of recurrent UTIs and renal damage in these patients.

2. METHODS

Medline (1966 to June 2008), Embase (1988 to June 2008), and Cochrane Central Register of Controlled Trials were searched using the combined search terms "vesicoureteral reflux" (MeSH) and "antibiotic prophylaxis" (MeSH). National Guideline Clearinghouse, NICE Guidance, and Cochrane Database of Systematic Reviews were searched using the search terms "vesicoureteral reflux" and "urinary tract infection in children." Reference lists of articles, reviews, and studies were searched for additional studies.

After the search was performed, the titles of all retrieved publications were screened. If the title indicating the paper was potentially relevant, the abstract was reviewed. The full paper was reviewed if the abstract suggested that the paper was indeed relevant. This process was performed by one reviewer (MC Michiel Costers) and thereafter validated by two other reviewers (GB Guy Bogaert and RVDL Rita Van Damme-Lombaerts).

Five uncontrolled studies evaluated the effect of stopping antibiotic prophylaxis in this patient group [15–19].

Five randomized controlled trials (RCTs) and one cohort study that compared antibiotic prophylaxis with no treatment (i.e., surveillance with intermittent therapy of episodes of UTI) for children with VUR were included in this review [20–25].

Two Cochrane systematic reviews and two guidelines on the topic of antibiotic prophylaxis for children with VUR were identified [12, 26–28]. Instead of performing a meta-analysis on this limited number of RCTs, we present the results of these studies.

3. RESULTS AND DISCUSSION

Long-term antibiotic prophylaxis remains a common practice in the management of children with VUR. The most commonly used drugs are nitrofurantoin, cotrimoxazole, amoxicillin, and cephalosporins [29, 30]. However, these medications may cause side effects and promote the development of resistant bacteria [22, 23, 25, 31]. Furthermore, the optimal duration of prophylaxis and optimal (low) dose of antibiotic are unclear, and compliance with this long-term treatment is not always assured.

In the 1960's, animal data showed that a UTI in the presence of VUR can cause renal damage. It was then hypothesized that sterilization of the urine could prevent pyelonephritis, and thereby also the resulting parenchymal damage.

At the end of the 1970's, two very small studies indeed suggested that prophylactic antibiotics may prevent recurrent UTIs in children, particularly during the period of prophylaxis. Smellie et al. [32] compared 6–12 months of antibiotic prophylaxis (cotrimoxazole or nitrofurantoin) versus no treatment in 53 children with acute UTI. None of the children in the intervention group had a UTI during the prophylaxis period, while 11 children in the control group presented with a UTI. Twelve months after stopping prophylactic antibiotics, 8 children (32%) in the intervention group compared with 13 (64%) in the control group had suffered from a recurrent UTI.

Lohr et al. [33] performed a crossover study on 18 girls with a history of at least 3 episodes of bacteriuria in the previous year (including 1 girl with VUR). Each child was placed on nitrofurantoin for 6 months and on placebo for a similar period. There were 35 episodes of bacteriuria (4.2 episodes/patient/year) in the patients taking the placebo versus 2 episodes (0.2 episodes/patient/year) in the children taking the antibiotic. Fourteen symptomatic UTIs (1.7 episodes/patient/year) occurred during the placebo periods, and none during the prophylaxis periods.

In 1997, the Pediatric Vesicoureteral Reflux Guidelines Panel of the American Urological Association (AUA) recommended continuous antibiotic prophylaxis as initial therapy for children with reflux grades I–IV [28]. However, this recommendation was based on expert opinion rather than on clear scientific evidence.

3.1. Discontinuation of antibiotic prophylaxis

During the following decades, this therapeutic practice has been challenged on multiple occasions. First, several authors demonstrated that in certain circumstances antibiotic prophylaxis can be safely discontinued.

Cooper et al. [15] discontinued antibiotic prophylaxis in 51 children with persistent primary VUR (grades I–IV). All children were old enough to describe the symptoms of UTI (mean age at stop of antibiotics = 8.6 years), and had a minimal or questionable history of true UTI, normal voiding patterns, and kidneys with no significant hydronephrosis or scars. A retrospective chart review revealed 6 episodes (11.8%) of UTI after cessation of prophylaxis (mean follow-up off antibiotics = 3.7 years): 1 case of cystitis and 5 cases of clinically presumptive pyelonephritis. None of the children showed new renal scars on renal ultrasound. However, it should be noted that renal ultrasound has low sensitivity for detection of renal scars.

The retrospective chart review by Thompson et al. [16] of 196 children (mean age at stop of antibiotics = 6 years) who had been withdrawn from prophylactic antibiotics (mean follow-up off antibiotics = 3.4 years) despite persistent reflux (all grades) showed a similar rate of UTIs per patient/year on or off antibiotics (0.29 on versus 0.24 off). Paradoxically, for the 39 children with high-grade reflux IV or V, there was a difference in the rate of UTIs per patient/year seemingly in favor of discontinuation of antibiotic prophylaxis (0.39 on versus 0.18 off). In addition, the rate of new renal scarring on DMSA scan after stop of antibiotics was comparable with the rate during prophylaxis (2.6% on versus 3.6% off).

Hellerstein and Nickell [17] followed (mean follow-up of 3.7 years) 66 children (mean age at stop of antibiotics = 4.4 years for the girls and 3.1 years for the boys) considered at risk for UTI (including 48 children with VUR) after completion of the initial course of prophylactic antibiotics. During the initial course of prophylactic antibiotics, 16 children presented with UTIs, with voiding dysfunction and abnormal kidney(s) being identified as risk factors for these infections. Twenty-eight children had UTI during the follow-up period, but 13 of these children were receiving an antibiotic at the time of the infection. Voiding dysfunction was again identified as a risk factor for infection in this time period.

Al-Sayyad et al. [18] also performed a retrospective chart review of 78 children of 4 years or older with persistent VUR (mean age at stop of antibiotics = 5.7 years) and with reflux grade less than IV and normal voiding pattern or mild voiding dysfunction, who were taken off antibiotic prophylaxis (mean follow-up off antibiotics = 37.7 months). UTI developed in 9 children (11.5%): 8 cases of cystitis and 1 case of clinically presumptive pyelonephritis. None of the children had new renal scarring detected on renal ultrasound.

Fifty-four children (mean age at stop of antibiotics = 6 years) with persistent VUR (all grades, but only 2 patients had high-grade reflux IV or V at the stop of antibiotics) were followed prospectively after discontinuation of antibiotic prophylaxis (mean follow-up off antibiotics = 4.4 years) in the study by Georgaki-Angelaki et al. [19]. All these children were old enough to describe symptoms of UTI, and had normal voiding patterns, kidneys without hydronephrosis or new scar lesions, and a period of at least 2 years without UTI. The number of symptomatic UTI episodes was similar during the on- and off-prophylaxis periods: 9 (cystitis 3 and pyelonephritis 6) and 8 episodes (cystitis 1 and pyelonephritis 7), respectively. No new scars were detected by DMSA scan at the end of the prophylaxis period (50 children tested) and at the end of the follow-up period (33 children tested). In none of the children, renal function deteriorated.

3.2. Antibiotic prophylaxis versus intermittent therapy of episodes of urinary tract infection

The small studies by Reddy et al. [20] and Craig et al. [21] were the first to compare antibiotic prophylaxis with no treatment. In the study by Reddy et al. [20], 43 children with VUR were randomly assigned to one of three groups: daily urine nitrate tests without antibiotic prophylaxis (surveillance), daily urine nitrate tests with antibiotic prophylaxis 3 times a week (intermittent prophylaxis), or daily antibiotic prophylaxis (continuous prophylaxis). The incidence of UTI in the 3 groups was as follows: 1/13, 2/14, and 5/16 in the continuous prophylaxis, intermittent prophylaxis, and surveillance groups, respectively.

In the study by Craig et al. [21], 41 children under 3 months of age with asymptomatic VUR received antibiotic prophylaxis (cotrimoxazole for 3 years) or placebo. Two children in the placebo group ($n = 20$) and no child in the antibiotic group ($n = 21$) developed UTI, and none of the children developed new renal damage on DMSA scan.

The multicenter study of Garin et al. [22] evaluated the role of VUR in causing UTI and renal parenchymal damage in 218 patients after an episode of acute pyelonephritis, and determined whether antibiotic prophylaxis (nitrofurantoin or cotrimoxazole for 1 year) could prevent UTI and renal parenchymal damage in the subgroup of patients with mild or moderate VUR (grades I–III). After 1 year of follow-up, the presence of VUR did not significantly increase the incidence of UTI or renal scarring on DMSA scan. Among the 113 patients with VUR, antibiotic prophylaxis did not result in a clinical advantage to prevent UTI (23.6% on versus 22.4% off prophylaxis) or renal scars (9% on versus 3.4% off prophylaxis). Ironically, recurrent acute pyelonephritis was more frequent in the intervention group than in the control group (12.9% on versus 1.7% off prophylaxis) and in all 7 cases, while on antibiotics the offending bacteria showed resistance to the used antibiotic.

In the updated meta-analysis for the Cochrane Database of Systematic Reviews [26], the authors stated that the studies by Reddy et al. [20] and Garin et al. [22] were unable to demonstrate a difference in the risk for UTI or renal parenchymal damage between intervention and control groups, and also that differences cannot be excluded because of the small number of patients studied so far. Furthermore, they concluded that combined therapy (antibiotic prophylaxis plus surgery) offers no advantages over antibiotic prophylaxis alone in terms of risk for UTI or renal parenchymal damage.

Conway et al. [23] studied a cohort of 611 children aged 6 years or younger with a first episode of UTI and without significant comorbidity to identify risk factors for recurrent UTI and examine the effect of antibiotic prophylaxis on recurrent UTI. Age of 3–5 years and high grade of reflux (IV or V) were identified as risk factors for recurrent UTI; the impact of voiding pattern was not evaluated in this study. They found that antibiotic prophylaxis had no significant effect on the risk of recurrence of UTI (hazard ratio of 1.01), even when stratified by type of antibiotic and stratified for covariates such as sex, race, age, and result of VCUG. Among the 83 children with recurrent UTI, a nested case-control study was performed to determine risk factors for isolation of resistant bacteria. Antibiotic prophylaxis clearly increased the likelihood of the infection being caused by a resistant pathogen (odds ratio of 7.50).

A French multicenter study by Roussey-Kesler et al. [24] evaluated whether antibiotic prophylaxis (cotrimoxazole for

18 months) could reduce the recurrence of UTI in 225 young children with grade I, II, or III VUR. Eighteen months later, recurrence of all UTIs and febrile UTIs was not significantly different between the intervention and control groups: 17% versus 26% ($P = .15$) and 13% versus 16% ($P = .52$), respectively. When patients with grades I–III reflux were analyzed separately, again no significant differences were observed ($P = .22$, $P = .23$, and $P = .57$, resp.). However, prophylaxis significantly reduced UTI in boys ($P = .013$) but not in girls ($P = .8$), and then only in those boys with grade III VUR ($P = .04$).

Finally, an Italian multicenter study by Pennesi et al. [25] assessed the effectiveness of antibiotic prophylaxis (cotrimoxazole for 2 years) in preventing pyelonephritis and in avoiding the occurrence of new scars in 100 children with grade II, III, or IV VUR at first episode of pyelonephritis, who were younger than 30 months. After 2 years of follow-up, 18 children (36%) in the intervention group and 15 children (30%) in the control group had at least 1 pyelonephritis recurrence. Thus, the risk for having at least 1 pyelonephritis recurrence was even slightly higher in the intervention group than in the control group (relative risk of 1.2). While all episodes of pyelonephritis in the control group were caused by sensitive strains of *Escherichia coli*, multiresistant bacteria (all resistant to cotrimoxazole among other antibiotics) were responsible for all infections in the intervention group. Furthermore, the presence of renal scars on DMSA scan was the same in children with or without antibiotic prophylaxis (relative risk of 1.2).

According to the recently revised NICE guideline, antibiotic prophylaxis is not routinely recommended in children after first-time UTI, and should only be considered after recurrent UTI [12, 13].

4. CONCLUSION

Despite the lack of evidence for its effectiveness, long-term antibiotic prophylaxis has been a common practice in the management of children with VUR for decades. However, several uncontrolled studies (total of 379 children) indicate that antibiotic prophylaxis can safely be discontinued in a subset of patients, that is, school-aged children with low-grade VUR, normal voiding patterns, kidneys without hydronephrosis or scars, and normal anatomy of the urogenital system.

More importantly, several recent RCTs suggest that antibiotic prophylaxis (with cotrimoxazole) offers no advantage over intermittent antibiotic therapy of UTIs in terms of prevention of recurrent UTIs or new renal damage. However, further research is still warranted in view of the limited number of children (total of 522 children) studied in these five RCTs. Furthermore, children with high-grade VUR have generally been excluded from these studies, and these findings cannot therefore be generalized. Finally, one of the RCTs indicates that boys with grade III VUR benefit from antibiotic prophylaxis, and there is a possibility that other subsets of patients, who will benefit from prophylaxis, will be identified in the future.

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Review Article

The Outcome of Surgery versus Medical Management in the Treatment of Vesicoureteral Reflux

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Evaluation of the relative merits of medical versus surgical management of vesicoureteral reflux (VUR) has been limited by the few prospective studies comparing these strategies. Among those trials that have been reported, the only consistent positive finding has been that incidence of febrile UTI is lower among children undergoing surgical treatment in comparison with medical treatment. Studies have not found significant differences in overall incidence of UTI, or in rates of new renal scarring or progression of existing scarring. It is likely that there is a subset of children with VUR who do benefit from aggressive treatment of their VUR, but we are not yet able to fully determine which children these are. It is hoped that future research will further clarify which treatments are useful in which children.

1. INTRODUCTION

Urinary tract infection (UTI) is one of the most common serious bacterial infections in children. Cumulative incidence is 1-2% among boys and 3–7% among girls, and between 70 000 to 180 000 of the annual US birth cohort will have a UTI by the age of 6 [1]. Roughly 30–50% of children with UTI are found to have vesicoureteral reflux (VUR, the retrograde flow of urine from the bladder into the ureter and/or kidney). Because VUR (particularly when coexistent with UTI) has been associated with increased risk of renal scarring, proteinuria, hypertension, eclampsia, and end-stage renal disease (ESRD) [2], children with UTI typically undergo diagnostic evaluation for and treatment of VUR.

In addition to its association with UTI, VUR is also a highly genetic condition, displaying an autosomal dominant transmission pattern, with variable penetrance. VUR may occur in up to 66% of the offspring of VUR patients [3], and the prevalence of VUR among siblings of index VUR patients is approximately 32% [4].

It has long been appreciated that there is an association between recurrent UTI, VUR and renal parenchymal scarring [5]. The traditional paradigm holds that once pathogenic bacteria establish infection in the bladder, the presence of VUR allows these bacteria to gain access to the upper tracts, invading the renal parenchyma and producing clinical acute pyelonephritis [6]. The resulting inflammatory cascade is presumed to result in tissue damage, fibrosis, and scarring in susceptible individuals.

In general, most management strategies for VUR have sought to address and defeat this process at various points along the pathogenic sequence. Medical management with antimicrobial prophylaxis seeks to maintain sterile urine, rendering the VUR itself relatively harmless, since there are no bacteria present to reach and invade the kidney. Antireflux surgery (ARS), in contrast, reconfigures the ureterovesical junction anatomy to block access to the upper tracts, so that any episodes of cystitis that do occur cannot progress to pyelonephritis.

However, this model has been called into question in recent years by data that challenges many of the assumptions of the VUR paradigm. Long-term studies show that renal scarring can occur in children without VUR, and that renal scarring is not common in children with even high degrees of reflux [7, 8]. Rushton et al. noted that new renal scars are formed less frequently after acute pyelonephritis in kidneys with VUR than those without VUR [9], and other studies have supported these findings to some extent [10]. End-stage renal disease and transplant registries maintained since the 1960's have not demonstrated the reduction in the

proportion of cases attributable to VUR that one would expect, if the management strategies instituted since that time were having a significant impact on rates of renal scarring and renal insufficiency [7, 11].

As we will see below, it has been difficult to demonstrate that current management strategies for VUR result in measurably improved outcomes. Since these management strategies are based on assumptions about the pathophysiology of UTI, VUR, and renal scarring, if such assumptions are incorrect then it should not surprise us that our interventions seem to have little or no effect.

2. MEDICAL MANAGEMENT

The use of antimicrobials to reduce recurrent and/or chronic UTI's dates back to the 1940's and 50's, and is the mainstay of initial management in children diagnosed with VUR. Based on the perception that antimicrobial prophylaxis is safe, effective, and easily tolerated, generations of children with VUR have spent years undergoing this treatment while awaiting the spontaneous resolution of their VUR. The classic studies of Smellie et al. form much of the basis for prophylaxis as a management tool [2, 5, 12]. In their numerous series, the Smellie group made seminal observations regarding the associations between VUR, UTI, and negative renal outcomes including scarring and decreased renal growth, and developed hypotheses regarding the apparent benefits of antimicrobial prophylaxis in children with VUR. They noted that children on continuous antimicrobial prophylaxis seemed to have fewer recurrent UTI than those on intermittent antibiotics, that children who stopped antibiotics seemed to be prone to recurrence shortly thereafter, and that increasing number of infections was associated with increased risk of renal scarring. Although groundbreaking, these data were based on nonrandomized, retrospective reviews, and thus do not adequately control for confounding factors and bias.

As a consequence, antimicrobial prophylaxis lacks basic evidence of efficacy in prevention of either UTI or renal scarring. Three randomized controlled trials comparing antimicrobial prophylaxis with no treatment (surveillance only) have been reported [13–15], and one of these was published in conference proceedings only [14]. None of the trials found significant differences in rates of UTI or renal scarring in treatment versus nontreatment groups. In the most recent study [15], subjects were kept on antimicrobial prophylaxis or no treatment for 2 years, and then were followed off medication for an additional 2 years. There were no differences in UTI rates either at the 2-year or 4-year mark. A recent population-based study using administrative data in a group of 611 children with UTI (27% of whom had VUR) found that the use of antimicrobial prophylaxis was not associated with decrease in risk of recurrent UTI [16]. Although each of these studies has methodological problems, the failure of any of them to find any effect of antimicrobial prophylaxis in preventing UTI suggests that the effect, if any, is likely to be very small. This, in turn, suggests that large number of children need to be treated for any single child to experience the benefits of prophylaxis.

3. SURGICAL MANAGEMENT

Since the initial report of surgical correction of VUR by Hutch in 1952 [17], numerous techniques have been developed to accomplish the basic goals of ARS, that is, prevention of retrograde flow of urine into the ureter and kidney. In fact, many of the leading figures in the development of the specialty of pediatric urology made their names largely through their accomplishments in perfecting ARS techniques. Today, in expert hands, the success rate of straightforward ARS approaches 100%, such that some surgeons no longer bother with post-ARS cystography to confirm VUR resolution [18–20].

The extraordinary success of modern ARS might lead one to assume that there is little room left for technical innovation in this field. However, investigators have long sought a less invasive way to correct VUR. In 1981, the first injection technique was reported by Matouschek using polytetrafluoroethylene (PTFE; Teflon) paste [21]. Concern over migration of PTFE particles to distant body sites [22] limited the popularity of this bulking agent in the United States, but in 1995, a Swedish group reported development of a dextranomer copolymer/hyaluronic acid gel for use as an injectable bulking agent (DX/HA; Deflux) [23]. The FDA approved Deflux for correction of VUR in 2001, and since then its use has increased significantly in many parts of the US [24] , with reported VUR resolution rates of 68–89% [25–28].

To our knowledge, there have not been any prospective trials of surgical management compared with observation in children with VUR. Therefore, we simply do not know if ARS is superior to surveillance alone in prevention of UTI or renal scarring. Because active management of VUR (either with antibiotics or surgery) is considered standard of care, it is difficult to find patients who have truly been given no treatment for their VUR, even in a retrospective review.

4. COMPARISON OF SURGICAL VERSUS MEDICAL MANAGEMENT

Comparison of medical treatment with surgical treatment for VUR is challenging because the different studies have used various outcome measures, and even studies using similar outcome measures may be difficult to compare due to differing definitions of similar outcomes. Reported outcomes in many studies include postoperative incidence of any UTI, incidence of febrile UTI (presumed in most cases to be equivalent to pyelonephritis), and renal cortical abnormalities (scarring).

In a recent metaanalysis of clinical trials, Hodson et al. identified seven randomized controlled trials comparing surgical and medical management [29–35] and summarized their results [36].

4.1. Any UTI

There was no difference in incidence of any UTI between treatment groups, with incidence of 29–42% in antibiotic only group and 25–40% in the surgical group [29–35]. Thus,

surgical treatment of VUR does not seem to reduce the rate of UTI overall.

4.2. Febrile UTI

Reported in only 2 studies, this is the only outcome where significant differences in outcomes have been observed between treatments [31, 37]. The surgical group had significantly fewer febrile UTI's in short-term and long-term followup [32], with relative risk of febrile UTI during the first 5 years of 0.43 (95% CI: 0.27–0.70).

4.3. Renal scarring

In the five studies that assessed renal parenchymal abnormalities using IVP criteria [29–31, 33, 38], there were no significant differences noted between surgical and medical groups. The majority of these studies assessed renal abnormalities using IVP. In the two studies that reported DMSA renal scintigraphy [35, 39], there was no difference in either progression of existing scars or development of new scars.

4.4. Future directions

There is little strong evidence supporting the hypothesis that early detection and treatment of VUR is of any benefit, primarily because it has been so difficult to demonstrate any benefit from the available therapies. Perhaps the one firm conclusion we can draw from the literature described above is that, among children with VUR who have had breakthrough febrile UTI's while on antimicrobial prophylaxis, ARS is an appropriate therapy that can be expected to reduce the incidence of such febrile episodes. However, neither prophylaxis nor ARS can be reliably stated to reduce the risk of new or progressive renal scarring, although it is prevention of this outcome that is widely assumed to be the most important benefit of VUR treatment.

It is plausible that, while treatment of VUR may reduce the risk of negative outcomes in a small subset of VUR patients, the number needed to be treated (in order to realize those benefits); it may be so high as to make the intervention unjustified for the overall VUR population. For this reason, ongoing research into biomarkers that will indicate those at highest risk for recurrent infection and progressive renal damage is crucial; such biomarkers would allow us to narrow the field of candidates for medical or surgical treatment to those most likely to benefit, and allow the larger VUR population to escape the morbidity and bother associated with these treatments.

Finally, there has been much recent discussion about whether the availability of endoscopic ARS should alter the indications for ARS. Suggestions have begun to appear in the literature and at national meetings that endoscopic treatment should be utilized as initial therapy for patients diagnosed with VUR. Advocates argue that immediate endoscopic therapy is preferable to antimicrobial prophylaxis in children just diagnosed with VUR [40]. Current standards of care do not yet embrace such early treatment: Khoury and Bagli state in their textbook chapter that "the indications for correction of reflux should remain unchanged regardless" of technique [41]. Furthermore, the data shown above make it clear that immediate ARS (using any method) makes little sense: the only demonstrated benefit of ARS is the reduction in incidence of recurrent febrile UTI, and a majority of newly diagnosed patients with VUR (except those with high-grade VUR) will never experience a recurrent febrile UTI, regardless of treatment choice [13, 16]. Therefore, an algorithm that directs all newly diagnosed VUR patients into immediate surgical treatment (even if it is the "low morbidity" of endoscopic ARS) is destined to overtreat large numbers of children for whom there will not be measurable benefits.

Ongoing clinical studies will hopefully clarify some of the glaring shortcomings in our evidence base. The NIDDK-funded RIVUR study is a randomized trial of antimicrobial prophylaxis versus placebo in children with VUR and UTI [42]. Each subject is followed for 2 years during which incidence of UTI and renal scarring by DMSA criteria will be tracked. DMSA scans will be obtained at study entry, 1 year, and 2 years. Weaknesses of the study will include the broad range of subjects (intended to increase generalizability), including boys and girls, VUR Grade I-IV, ages 2 months to 5 years, and inclusion of trained and nontoilet trained children, with or without voiding dysfunction. Although the 2-year time frame is short, this large study (target sample $n = 600$) will provide us with superb data regarding risk of UTI and renal scarring in children with VUR in the short term, as well as demonstrate whether antimicrobial prophylaxis is effective in preventing either UTI or scarring. Other studies assessing the utility of ARS in various clinical scenarios are desperately needed. Until such studies are complete, clinicians who treat children with VUR will continue to rely on clinical judgment, experience, and intuition to manage their young patients.

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Review Article

Vesicoureteral Reflux and Duplex Systems

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Vesicoureteral reflux (VUR) is the most common anomaly associated with duplex systems. In addition to an uncomplicated duplex system, reflux can also be secondary in the presence of an ectopic ureterocele with duplex systems. Controversy exists in regard to the initial and most definitive management of these anomalies when they coexist. This paper will highlight what is currently known about duplex systems and VUR, and will attempt to provide evidence supporting the various surgical approaches to an ectopic ureterocele and duplex system and the implications of concomitant VUR.

1. INTRODUCTION

Less than 1% of the general population has a duplex kidney [1]. Females are affected more commonly than males and this anomaly is bilateral in 17–33% of cases [2]. VUR is the most common associated anomaly found in duplex kidneys and is present in 70% of these patients who present with a urinary tract infection [3, 4]. VUR almost always occurs into the lower-pole moiety due to its lateral displacement within the bladder. If VUR is seen in the upper-pole moiety, one must suspect a laterally displaced incomplete duplication or an ectopic orifice located within the bladder neck or urethra. This paper will review the natural history of VUR associated with uncomplicated duplex systems as well as the controversies that arise in managing reflux found in conjunction with ectopic ureteroceles.

2. DISCUSSION

2.1. VUR and duplex systems

There are certain factors that contribute to reflux resolution in single-system (SS) ureters, including patient age, grade of reflux, postnatal presentation, and the presence or absence of associated voiding dysfunction [4]. The natural history of VUR in association with duplex systems (DSs) is not completely clear. Despite several studies addressing this issue, all were limited in some way by their noncontrolled retrospective nature, patient selection or surgeon bias, and limited long-term follow-up [4]. Lee et al. followed 1/3 of their patients with VUR and DS nonoperatively, and concluded that resolution rates of low-grade (I-II/V) reflux were comparable to those seen in SS [5]. Patients with high-grade reflux were excluded from this study. A similar conclusion was noted in another study in which all grades of reflux were included. Spontaneous resolution occurred in over half of patients with grades I–III/V VUR and support consideration for initial conservative management with prophylactic antibiotics [6]. Over a two-year period of observation, Husmann et al. found that reflux resolved in 10% of patients with DS and grade II/V VUR as compared to 35% of a matched group of patients with SS; however, there were no differences in the incidence of breakthrough infections, additional renal scarring, or worsening reflux [7]. It seems clear that most patients with DS and low grades (<III/V) can be initially managed conservatively; however, VUR will likely take longer to resolve as compared to SS VUR. Clinical information concerning high-grade VUR (IV-V) and DS is lacking, although one study documented no resolution at mean follow-up of 42 months as well as an increased incidence of infectious complications, especially in young females [4].

Data from the available literature suggests that the majority of patients with DS and low-grade VUR can be initially managed with antibiotics and careful observation. Parents

should be counseled that it may take longer for the reflux to resolve and young females with high-grade VUR may be at increased risk for infections. Despite these findings, the absolute indication for surgery in individuals with low-grade VUR is not different from those with SS and similar VUR, and surgical correction is successful in the majority of cases [4]. In fact, one series reported a 98% success rate for common sheath reimplantation of uncomplicated duplex systems, and concluded that the presence of a duplication anomaly does not adversely affect surgical outcome. Adequate tunnel width and long intravesical tunnels were noted to be the most important technical aspects [8]. It is important to remember, however, that complicated duplex systems associated with the need for ureteroureterostomy, ureteral tapering or tailoring, or ureteropyelostomy may carry higher complication rates than uncomplicated common sheath reimplantation.

2.2. Ectopic ureteroceles and vesicoureteral reflux

Duplex systems are an uncommon diagnosis causing prenatal hydronephrosis; however, when confirmed, ureteroceles are one of the most common associated findings [9, 10]. Ectopic ureteroceles can cause upper-pole hydronephrosis and obstruction, which leads to ipsilateral lower-pole reflux in 50% of cases [11]. Contralateral reflux is seen in 25% of cases and reflux into the ureterocele occurs 10% of the time [12].

The initial and subsequent management of ureteroceles has been controversial and depends on several factors, including presenting symptoms, ectopic versus orthotopic position, presence or absence of reflux, and function of the associated upper-pole moiety [11]. As the focus of this article is reflux and duplex systems, the discussion below will be limited to the management of ectopic ureteroceles in patients who present with concomitant reflux and a nonfunctioning or functioning upper-pole moiety. Management options include endoscopic puncture and decompression, a simplified upper-tract approach, namely, heminephrectomy, or complete repair including upper-pole surgery, ureterocele excision, and lower-tract reconstruction in a single setting.

In the above proposed setting, the clear indication for endoscopic decompression of an ectopic ureterocele is in a child who presents with sepsis or bladder outlet obstruction. However, in the setting of sepsis, one must open the ureterocele completely, as puncturing may not result in adequate drainage. This procedure almost invariably results in prompt improvement in patient symptoms, but the parents should be counseled that their child will require definitive reconstruction at a later date, as reflux into the upper-pole moiety is the rule, not the exception. In contrast, endoscopic puncture of an ectopic ureterocele in the nonemergent setting may also commit the patient to future reconstruction. In one series describing endoscopic puncture for ectopic ureteroceles, Jayanthi et al. reported postoperative reflux into the upper-pole moiety in 50% of cases [13]. Overall, 70% of their patients underwent open surgery with the vast majority at the level of the bladder [13]. Some have argued that initial endoscopic decompression may facilitate subsequent lower-tract surgery by reducing the size of the upper-pole ureter [14].

Upper-pole heminephrectomy can result in excellent decompression of the ureterocele and should be the procedure of choice if there is no ipsilateral lower pole or contralateral reflux [15]. Removing a functional upper pole has been advocated by some as this moiety only provides approximately 15% of total renal function at best [16]. Alternatively, one can salvage the upper pole with a ureteroureterostomy or ureteropyelostomy and subtotal ureterectomy. Success of the upper-tract approach alone without the need for subsequent bladder surgery is directly related to the presence or absence of ipsilateral lower pole or contralateral reflux. Husmann et al. reported a definitive cure in only 16% of patients in this setting if endoscopic decompression or an upper-tract approach was used alone. In fact, the need for additional surgery was related to the number of renal moieties with reflux at presentation, reporting a 96% reoperative rate with unilateral high-grade reflux or reflux seen in more than one renal moiety [16].

In conclusion, ectopic ureteroceles that reflux or are associated with reflux into other moieties are likely best served with ureterocele excision or marsupialization, bladder floor reconstruction, and ureteral reimplant. Another option would be a ureteroureterostomy with a lower-pole extravesical reimplant. In those patients who present with sepsis or bladder outlet obstruction, endoscopic decompression is highly successful but will likely commit the patient to further surgery. Upper-pole heminephrectomy is best applied to those patients with nonfunctioning upper poles and no associated reflux. In this setting, this approach is highly successful and has the advantage of avoiding bladder surgery, limiting risks to the lower pole, and eliminating the potential unknown risks of preserving a dysplastic upper pole [15]. Arguably, upper-pole heminephrectomy can be performed open or laparoscopically.

3. CONCLUSIONS

Reflux found in association with a duplex system may take longer to resolve than single-system reflux. Parents should be counseled accordingly. Surgery to correct VUR in duplex systems is highly successful. Ectopic ureteroceles can present an interesting and difficult surgical challenge and can be ultimately managed with multiple surgical approaches following initial conservative therapy. Endoscopic decompression seems best reserved for the septic patient or one who presents with bladder outlet obstruction. It provides excellent relief of obstruction and can preserve upper-pole renal function. Ultimately, these patients are currently managed by either an upper- or lower-tract approach. The most important factor in deciding which approach to take is the presence or absence of VUR.

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Review Article

Treatment of Vesicoureteral Reflux after Puberty

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Vesicoureteral reflux is uncommonly diagnosed and treated after puberty. The natural history of uncorrected VUR after puberty is not documented. Postpubertal patients with recurrent pyelonephritis and VUR should be considered for treatment. Ureteral reimplantation, endoscopic injections, and laparoscopic or robotic ureteral reimplantation may be utilized. Endoscopic injection is an appealing option for these patients. The role of laparoscopic or robotic ureteral reimplantation in these patients is evolving.

1. INTRODUCTION

Vesicoureteral reflux (VUR) is a common finding in children with urinary tract infections (UTIs). The incidence of VUR associated with UTIs drops significantly in older children, particularly after the age of 5 [1]. It has been a long-held dogma of pediatric urology that unresolved VUR should be treated before a child progresses through puberty. There is concern that females with uncorrected VUR will have problems with pyelonephritis when they become sexually active and during pregnancy. Pyelonephritis during pregnancy increases the risks of the pregnancy and possibly to the unborn child as well. If these children have their reflux corrected before they go through puberty, these problems could be prevented. While in theory this justifies the surgical correction of all children who fail to resolve their reflux during a period of observation, there is little evidence to support treating all children and no long-term studies documenting the natural history of uncorrected VUR after puberty. This manuscript will review the association of VUR and UTIs in patients treated after puberty and examine the role, nuances, and outcomes of treating VUR after puberty.

2. CLINICAL IMPORTANCE OF VUR AFTER PUBERTY

There has been a long-standing observation of the association of febrile UTIs and the development of renal scarring [2]. The riskiest time for the development of renal scarring due to febrile UTI associated with primary VUR is infancy and the risk of developing new scars drops significantly after age of 5 [3]. It is still common to follow and treat patients beyond this age. While severe scarring may predispose to chronic kidney disease in a small percentage (estimated at 2%), the majority of children with VUR are not at significant risk for renal failure [4]. There is a higher incidence of hypertension in patients with renal scarring, but severe complications due to VUR are unusual. The only reliable benefit to patients who's VUR is surgically corrected is a decreased risk of pyelonephritis, but the incidence of UTIs is similar to those who reflux has persisted. These findings have led some to consider stopping antibiotic prophylaxis in selected children and ceasing surveillance for resolution [5, 6]. Voiding cystourethrograms (VCUG) can be perceived as traumatic by children and simplifying their follow-up and avoiding these tests may be a major factor in discontinuing follow-up for some parents. As a result of these practices more and more physicians are going to allow children with persistent VUR to continue through puberty with uncorrected VUR. As a group, these patients will likely have lower grades of VUR, infrequent UTIs, and normal renal function. There are currently no longitudinal studies documenting just what risks these patients will face and whether their VUR will be a significant problem during adolescences and adulthood. It is likely that some of these patients will have future problems with UTIs and be considered for treatment of their VUR after puberty.

There has also been a change in VUR management by some pediatric urologists that is the polar opposite of

stopping prophylaxis and observing patients. Instead of following patients for resolution of their VUR, primary therapy with endoscopic injections after the diagnosis of VUR is being offered [7]. Touted as a minimally invasive alternative, the "15-minute cure" is being used as upfront therapy in patients after diagnosis to avoid the need to prolonged antibiotic prophylaxis and prolonged follow-up while waiting for the VUR to resolve. While success rates greater than 90% are reported by experienced surgeons, the follow-up in these series is generally short with VCUGs being performed usually within 3 months of the procedure [8]. There is a known rate of relapse for this method which is highest for collagen, and was reported to be greater than 50% at 5 years [9]. The relapse rate is lower for other agents [10, 11]. If there is a 10–15% relapse over 5–10 years (a reasonable estimate given the few long-term studies available) it is likely that there will be increasing numbers of late failures of endoscopic therapy. Of these patients, some will present after puberty with pyelonephritis and recurrent VUR.

3. VUR AND UTIs AFTER PUBERTY

The primary motivation for treatment of VUR before puberty has been over concerns of increased risk of UTIs when female patients become sexually active or pregnant. To my knowledge, however, the natural history of women with persistent VUR during pregnancy has not been documented. Pyelonephritis is a known risk to pregnant women and strongly associated with bacteruria. Large series have reported rates of 2% of pregnant women [12]. In pregnant women with a history of VUR or surgically corrected VUR, higher rates of UTIs and pyelonephritis have been reported. Mansfield et al. reported complications during pregnancy for patients who had undergone surgical correction of VUR and a group with a history of VUR that did not undergo surgery [13]. The rate of cystitis and pyelonephritis was 22% and 18%, respectively, during pregnancy for the patients with surgically corrected VUR. These rates were higher than the patients without treatment of their VUR with cystitis in 15% and pyelonephritis in 1.5%. They also reported a high rate of UTIs with the onset of sexual activity in 75% of patients with surgically treated VUR and 62% of those with a history of VUR that was not treated. There is a significantly increased risk of UTIs in women with a history of VUR. There could be multiple explanations for the differences in the two groups including that the surgical procedure is the cause of the increased UTIs. Due to the retrospective nature however, the authors point out that this observation of higher rates of UTIs in the surgically treated patients does not prove that the problem is due to the surgery. Other factors may be responsible for these differences, such as selection bias. These patients likely had an increased susceptibility to UTIs, which is likely what pushed them to surgical correction in the first place. The authors recommend that pregnant women with a history of ureteral reimplantation surgery undergo frequent screening for bacteruria during pregnancy and that prophylactic antibiotics be considered in these patients. Other series of long-term follow-up of patients with VUR treated with ureteral reimplantation surgery have similar findings. Beetz et al. reported a 25-year follow up in 158 patients [14]. Female patients reported subsequent UTIs in 74% after surgery versus 10% of males. 17% developed UTIs during pregnancy, however, they did not report whether these patients had pyelonephritis or cystitis. Of the UTIs, most (66%) were afebrile versus preoperatively where the UTIs were febrile. It remains unknown as to whether patients experiencing continued problems with UTIs after surgery would have fewer problems if they had not undergone surgery.

4. WHICH PATIENTS SHOULD BE EVALUATED AND TREATED?

The incidence of VUR after puberty is significantly lower than in young infants with febrile UTIs [1]. It has been well established that VUR is a risk factor for pyelonephritis and that it frequently is present as one of several risk factors for UTIs. Voiding dysfunction must always be considered in this patient population and treated appropriately. With proper treatment and modification of risk factors such as infrequent voiding, dysfunctional voiding, constipation, and incomplete emptying the VUR may be eliminated without surgical treatment [15].

Most postpubertal patients with VUR will present with UTIs. Since the majority of patients will not have VUR and assuming that VUR is an important risk factor for pyelonephritis, what are the factors that should prompt an evaluation for VUR in a postpubertal patient? First and foremost should be a history of recurrent febrile urinary tract infections, as these patients if found to have reflux, have a good chance of having their symptoms alleviated if VUR is found and treated. Suspicion should be raised if there is a history of prior VUR, febrile infections as a young child, or a family history of VUR. Due to the high association of renal scarring and VUR, patients who have a history of recurrent febrile UTIs and evidence of renal scarring on imaging studies should be evaluated for VUR. To evaluate for VUR a standard VUCG may be performed, or if there are symptoms worrisome for voiding dysfunction a videourodynamics study. In patients with evidence of renal scarring or a small kidney on ultrasound, a DMSA renal scan should be obtained to evaluate for renal scarring and the differential function. Typically, the grade of VUR is an important factor for predicting resolution and risk of renal scarring; however, in postpubertal patients it has not been studied as extensively. It is expected that the rates of spontaneous resolution will be lower after puberty.

5. SURGICAL TREATMENT OF VUR AFTER PUBERTY

One of the more humbling experiences for a pediatric urologist is their first ureteral reimplantation done on a female after puberty. These difficulties start as females approach puberty. During puberty, the pelvis widens and deepens in the female. The trigone assumes a deeper retropubic location which makes access to the ureteral orifices and the mobilization of the ureters more difficult. Additionally, the

plexus of vein running across the surface of the bladder enlarge and are more prone to troublesome bleeding during ureteral dissection. Though not well documented, most pediatric urologists would agree that, if a child truly needed ureteral reimplantation for correction of their VUR, then the operation is best performed if they are operated on during childhood rather than after puberty. Experience would tell us that they recover quicker and that technically the surgery should be more successful, however, there are not series documenting poorer results after ureteral reimplantation for patients treated after puberty. Options for treatment of VUR in patients after puberty include intra- or extravesical ureteral reimplantation, endoscopic injection, and laparoscopic or robotic reimplantation. In patients with unilateral VUR to a poorly functioning kidney nephrectomy may be an alternative choice to ureteral reimplantation. This can be performed laparoscopically with rapid recovery and short hospitalization.

6. URETERAL REIMPLANTATION

As mentioned previously, the postpubertal changes in women make the surgical access to the trigone more challenging and limit exposure; however, ureteral reimplantation can be performed in women successfully. In males, the changes are less dramatic. Published results of ureteral reimplantation in postpubertal patients are sparse due to the limited number of patients in whom this surgery is indicated. From a technical standpoint, it is prudent to position the patient over the break in the OR table. This allows the table to be flexed if necessary to open the pelvis and improve retropubic exposure. This is similar to the positioning of a male undergoing radical retropubic prostatectomy. The size and body mass index will play a role with obese patients creating more difficulties with exposure. Proper surgical planning and the use of larger and more flexible fixed retractors such as a Bookwalter rather than the Denis-Browne retractor will facilitate the procedure. Both ureteral advancements and ureteroneocystotomy procedures (e.g., Cohen, Glenn-Anderson, and Politano-Leadbetter) can be performed but limited data is available on their use in the treatment of VUR postpuberty [16–20]. There have been reports of the use of trigonoplasty (Gil-Vernet) procedures, which in postpubertal patients offer the advantage of less dissection and mobilization [21, 22]. Success rates of up to 97% have been reported but follow-up is limited to only 11 months.

7. ENDOSCOPIC INJECTION

Although controversy remains about the role of endoscopic injection for VUR as an alternative to ureteral reimplantation in young children, there are few "reimplanters" who would completely dismiss this option in patients after puberty. This technique has been practiced for over 20 years and a variety of bulking agents have been injected including polytetrafluoroethylene paste, gluteraldehyde cross-linked bovine collagen, polydimethysiloxane, and detranomer/hyaluronic acid copolymer (D/HA) [23]. In the United States the D/HA copolymer is the only agent that has been FDA approved for use in children. A recent series by Okeke et al. reported 9 women (mean age of 26) with symptomatic VUR associated with acute pyelonephritis who were treated endoscopically with D/HA [24]. All were treated successfully with no reflux by VCUGs at 3 months postoperatively, although 1 did require a second injection for persistent VUR. Two patients had transient flank pain immediately postoperatively which resolved after a few days. At a mean follow-up of 14 months, none of the patients had further infections or symptoms. In children, the treatment of VUR with D/HA injections has been associated with a lower incidence of UTIs postoperatively [25]. It is unknown whether or not postpubertal patients are at the same risk for late failures of endoscopic injection as was described in some of the original series of children.

8. LAPAROSCOPIC AND ROBOTIC URETERAL REIMPLANTATION

Minimally invasive ureteral reimplantation for VUR has been performed for over a decade; however its widespread uses have been slow to spread. Proponents of laparoscopic surgery would cite the limited laparoscopic experience of most pediatric urologists as a primary factor for this slow adaptation. However, many would argue against relearning to do a procedure which has rapid recovery, high success rate, low complication rate, and is done through an inconspicuous incision. A low, transverse abdominal incision leaves a scar that often blends into the natural creases of the abdominal skin leaving a barely visible mark. If placed low enough it is covered by undergarments and is not disfiguring. Given the questionable benefits and technical difficulties the laparoscopic technique has been slow to gain acceptance. One population where this approach actually may be a real asset is in treating VUR after puberty.

Both intra- and extra-vesical laparoscopic techniques for reimplantation have been described in children [26–28]. In the postpubertal female, the advantage for laparoscopy is that the scope and instruments can reach deep into the pelvis with good visualization. Shu et al. reported a series of laparoscopic extravesical reimplantations performed for VUR in postpubertal females at a mean age of 18 [29]. One patient underwent bilateral and the other 5 unilateral reimplantation. 1 patient had transient ureteral obstruction requiring a temporary stent placement. All had resolution of their VUR postoperatively.

Robotic assisted laparoscopic surgery has become a widely practiced urologic technique for performing radical prostatectomy [30]. The surgeons utilizing the robot for prostatectomies tout the increased magnification, 3D visualization, and precision movements the wristed instruments as advantages over the open surgical procedure. The neurovascular bundles are well visualized, as is the apical dissection of the prostate and urethra. Performing deep pelvic surgery such as ureteral reimplantation in postpubertal patients is a situation where the robotic approach may have an advantage over traditional open surgical reimplantation. There are limited reports of robotic ureteral reimplantations being

performed in children [31]. The robot allows a surgeon with good open surgical skills to perform complex laparoscopic procedures. Extravesical ureteral reimplantation has been associated with postoperative urinary retention when performed bilaterally [32]. This is felt to be due to injury to the pelvic plexus during the dissection of the ureter extravesically [33]. Casale et al. reported a series of 41 children with a mean age of 33 months treated with bilateral robotic "nerve-sparing" extravesical reimplantation [34]. All children voided well after catheter removal on postoperative day number 1. No patient had retention as documented by ultrasonic bladder scanning. Reflux was cured in 97% and no ureters were obstructed. If these impressive results can be achieved by other surgeons and applied to postpubertal patients, this could become the preferred approach to ureteral reimplantation surgery after puberty.

9. CONCLUSIONS

The natural history of untreated VUR in postpubertal patients is unknown. Treatment of VUR should be considered in those patients with VUR and recurrent febrile UTIs. The optimal method to treat VUR is not clear. Endoscopic injection is a minimally invasive approach which has a good success rate for treating VUR and offers some benefits over ureteral reimplantation. The role of laparoscopic and robotic ureteral reimplantation is evolving and may offer some advantages over open ureteral reimplantation in postpubertal patients.

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Review Article

Endoscopic Treatment of Vesicoureteral Reflux with Dextranomer/Hyaluronic Acid in Children

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Purpose. The goal of this review is to present current indications, injectable agents, techniques, success rates, complications, and potential future applications of endoscopic treatment for vesicoureteral reflux (VUR) in children. *Materials and Methods*. The endoscopic method currently achieving one of the highest success rates is the double hydrodistention-implantation technique (HIT). This method employs dextranomer/hyaluronic acid copolymer, which has been used in pediatric urology for over 10 years and may be at present the first choice injectable agent due to its safety and efficacy. *Results*. While most contemporary series report cure rates of greater than 85% for primary VUR, success rates of complicated cases of VUR may be, depending on the case, significantly lower. Endoscopic treatment offers major advantages to patients while avoiding potentially complicated open surgery. As the HIT method continues to be applied to complex cases of VUR and more outcome data become available, the indication for endoscopic treatment may exceed the scope of primary VUR. *Conclusions*. Endoscopic injection is emerging as the treatment of choice for VUR in children.

1. INTRODUCTION

Vesicoureteral reflux (VUR) is diagnosed in approximately 1% of children and promotes pyelonephritis, which may lead to renal scarring and hypertension [1]. VUR is one of many treatable risk factors (e.g., dysfunctional elimination) in the development of urinary tract infection (UTI). Treatment intends to prevent pyelonephritis and to preserve renal function and most children diagnosed with VUR receive antibiotic prophylaxis regardless of VUR grade [2]. Surgical management is indicated in cases of breakthrough UTIs and/or persistence of VUR and comprises ureteral reimplantation and endoscopic injection. Since the introduction of endoscopic treatment for VUR in 1981 and its first clinical application in 1984 as subureteric Teflon injection (STING), injection techniques, injectable agents, and consequently treatment success rates have considerably improved [3–6]. Endoscopic treatment not only approaches success rates of open ureteral reimplantation but offers also significant advantages to patients and parents such as outpatient surgery, lower morbidity (e.g., pain, scar), fewer complications, and reduced cost. Consequently, a major shift from reimplantations toward injection treatments has been observed over the last few years (Figure 1).

The purpose of this review is to summarize current indications, injectable agents, techniques, success rates, complications, and potential future applications of endoscopic treatment for VUR.

2. MATERIALS AND METHODS

2.1. Goals of treatment

There is little evidence that antireflux surgery of any means decreases the incidence of renal scarring or end-stage renal disease. Worthwhile goals of treatment are to prevent UTIs, particularly febrile UTIs, to avoid long-term antibiotic use, and to lessen the need for distressing voiding cystourethrographies (VCUG) and radiation exposure. Proponents of the endoscopic approach will argue that decreasing the incidence of UTI is the main goal of therapy. Recurrence, while possible, may occur in the absence of symptoms and

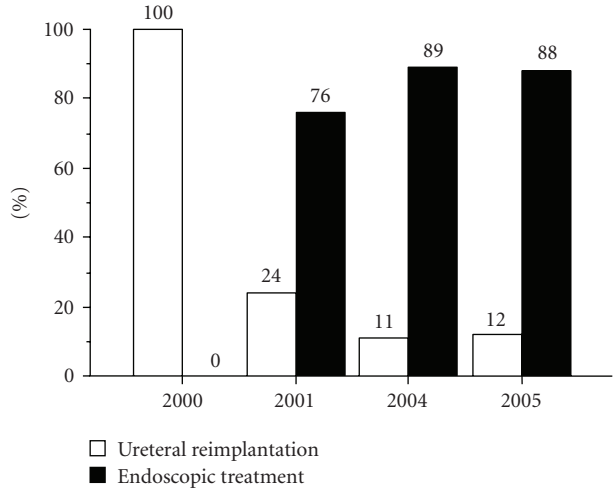

Figure 1: Trend of surgical treatment for VUR at Children's Healthcare of Atlanta from 2000 to 2005.

be viewed as subclinical, similar to an individual with VUR diagnosed after a sibling screen or for fetal hydronephrosis. Proponents of the open surgical approach will argue that ureteral reimplantation provides a permanent cure of VUR and is worth the increased morbidity to achieve this goal. In terms of reducing the risk of UTI, endoscopic treatment may achieve this goal as well or better than open surgery [7–9].

2.2. Indications

The indications for ureteral reimplantation and endoscopic treatment are with few exceptions identical and comprise recurrent UTIs despite antibiotic prophylaxis, persistent VUR after a period of observation (>2 years), poor compliance with antibiotic prophylaxis, and new renal scarring. When parents are counseled regarding surgical options, a significant preference for endoscopic treatment is apparent [10, 11]. Endoscopic injection has more frequently been employed for primary rather than for complex VUR (i.e., VUR associated with functional or anatomical abnormalities such as neurogenic bladder or ectopic or megaureters). Avoidance of endoscopic treatment for complex VUR is due to a paucity of supportive clinical data and the current view that bladder dysfunction and structural defects of the ureterovesical junction necessitate ureteral reimplantation. Endoscopic treatment is Food and Drug Administration (FDA)-approved for VUR grades II to IV and for cases of initial endoscopic treatment failure, however it has been applied to all VUR scenarios. While open ureteral reimplantation is the treatment of choice for failed injection therapy, endoscopic treatment has been successfully employed after failed ureteral reimplantation [12–14]. In general, endoscopic treatment is emerging as the treatment modality of choice for VUR whereas ureteral reimplantation remains reserved for cases of failed injection therapy, significant anatomical abnormalities (e.g., large paraureteral diverticula, ectopic ureters, megaureters), and surgeon's or parents' preference.

2.3. Injectable agents

Numerous injectable bulking materials have been utilized and abandoned over time in search for the ideal agent, which should be nonimmunogenic, noncarcinogenic, biocompatible, and biodegradable. Teflon, the first bulking material used for the treatment of VUR, was abandoned in pediatric urology in the USA because of the material's propensity to migrate to distant organs and to form granulomas; however, carcinogenesis of Teflon has not been reported [15–17]. Silicone also demonstrates distant migration and granuloma formation. Its carcinogenic potential has been controversial but is most likely unsubstantiated [18, 19]. Glutaraldehyde cross-linked bovine collagen demonstrates a lower degree of absorption as compared to native collagen and can cause allergic reactions even in patients with negative skin test [20]. Several new bulking agents are currently under investigation, such as inorganic materials and autologous tissue. The latter is nonimmunogenic, however, cell harvest and/or cell culture are time-consuming and expensive. Dextranomer/hyaluronic acid copolymer (Deflux, Q-Med Scandinavia Inc., Uppsala, Sweden) is easy to inject, is biodegradable with stable implant volume, and its relatively large particle size prevents distant migration [21, 22]. It has been used as injectable material in pediatric urology for over 10 years and is currently the first-choice injectable agent due to its safety and efficacy. Deflux implants in animal tissue were shown to undergo time-dependent histopathological changes. The initial phase was dominated by an ingrowth of granulation tissue, a foreign-body giant-cell reaction, and the formation of a surrounding capsule. In the later phase, cellular elements were largely replaced by a collagen-rich matrix, whereas the capsule remained unchanged [21]. These findings were confirmed in patients who experienced failed endoscopic injection and proceeded to ureteral reimplantation [22]. In our experience, explanted Deflux appears essentially unchanged up to 4 years after implantation. Besides biological properties, cost of bulking agents, and surgeon's experience, the choice may ultimately depend on approval by administrative agencies, such as the European Medicines Agency or the FDA.

2.4. Technique

The endoscopic method currently achieving one of the highest success rates is the double hydrodistention-implantation technique (HIT). Cystoscopy is performed with a pediatric cystoscope equipped with an off-set lens. An off-set lens permits direct passage of the needle in line with the ureter without bending the needle. The bladder is filled to less than half capacity to permit visualization of the ureter and avoid tension within the submucosal layer of the ureter secondary to overdistention. Hydrodistention (HD) is performed with the tip of the cystoscope placed at the ureteral orifice (UO), a pressured stream achieved by placing the irrigation bag approximately 1 meter above the bladder on full flow. HD of the distal ureter serves two purposes: it allows visualization of the intraureteral injection site and assessment of treatment progress (i.e., ureteral coaptation).

The needle is passed into the UO and inserted at the mid ureteral tunnel at the 6 o'clock position. Sufficient bulking agent is injected to produce a bulge, which initially coapts the detrusor tunnel, while a second implant within the most distal intramural tunnel leads to coaptation of the UO (approximately 1–1.5 mL). Rarely, if the two intraureteric submucosal injections (double-HIT method) fail to coapt the ureter, a classic STING or a supraureteric injection is needed to achieve coaptation. The latter two injection sites are used more commonly in complex or redo cases (Figure 2). HD is performed after each injection to monitor treatment progress; when HD ceases to dilate the UO, appropriate coaptation has been achieved. At our institution, all procedures are performed on an outpatient basis and all patients receive preoperative antibiotic prophylaxis, which is continued until resolution of VUR has been confirmed. Radiographic success is defined as grade 0 VUR on a postoperative VCUG, from 1 to 3 months after a single treatment. Patients are then followed clinically on an annual basis to determine clinical success and recurrence.

We have shown that the Deflux bleb size, determined by ultrasound, correlates with treatment success; a measured volume higher than 25% of the injected volume using the HIT method will result in a 90% cure and 95% using the double HIT method [23, 24]. Consequently, as part of a prospective clinical trial we are evaluating bladder ultrasounds from 4 to 6 weeks after endoscopic injection with measurement of the Deflux bleb. If the retained volume is >25%, antibiotics will be discontinued, no VCUG will be obtained until 1 year, and the patient will be followed clinically. An earlier VCUG will be obtained for volumes <25% or if clinically indicated. This protocol allows for the identification of clinically significant VUR and will evaluate the longer-term success rate. If the long-term VCUGs show favorable results and/or if patients do well clinically, the postoperative VCUG will be excluded in the future.

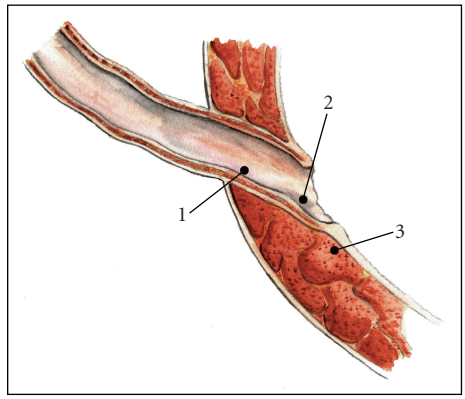

Figure 2: Needle placement algorithm for the endoscopic treatment of VUR. Sites 1 and 2 comprise the double-HIT method, while site 3 (STING) is rarely used.

3. RESULTS AND DISCUSSION

3.1. Success rates

Outcome of endoscopic treatment for VUR has been evaluated in several large series (Table 1). Most studies included both, primary and complicated cases of VUR. Interpretation of and comparison among these studies are confounded by different inclusion criteria (e.g., with or without complex VUR, grade I, grade V), varying lengths of follow-up, definitions of success, and single versus multiple injections. Nevertheless, most current series report cure rates of greater than 85%. Age, gender, and bilaterality of VUR have not been shown to predict treatment outcome. While the STING technique yields lower success rates with higher grades of VUR, the HIT method achieves similar outcomes across all VUR grades up to grade V [5]. Endoscopic treatment of complicated VUR has been evaluated in smaller series and success rates vary significantly depending on the associated pathologies (Table 2). In general, cure rates for complex cases of VUR are lower than for primary VUR. Treatment of VUR associated with neurogenic bladder was shown to yield acceptable outcome whereas voiding dysfunction was a significant predictor of treatment failure [13, 25]. Endoscopic injection has been successfully employed in patients who either failed ureteral reimplantation or initial injection [13, 14, 26]. Injection after failed reimplantion or second injection will be curative in most instances whereas a third injection has been shown to be far less successful [27, 28]. Refluxing ureters of transplanted kidneys in symptomatic patients may be treated endoscopically. Although this approach is curative in only half the cases, yet it represents an attractive alternative to open surgery in the setting of immune compromise and reduced wound healing properties [29]. VUR associated with anatomical abnormalities, previously thought to be contraindications for endoscopic treatment, was recently shown to be amenable to injection treatment [30–32].

There are many factors that may affect the success of the procedure. Preoperative (i.e., patient selection), intraoperative (i.e., injection technique), and postoperative variables have been shown to correlate with treatment outcome (Table 3). Postoperatively, failures may result from Deflux displacement (implant migration), disruption (mucosal breach), or dissolution (decrease in implant volume).

3.2. Advantages

In comparison to ureteral reimplantation, endoscopic VUR treatment offers major advantages to patients and parents. The procedure generally lasts less than 15 minutes and is performed on an outpatient basis. While cure rates are approaching those of open ureteral reimplantation, significant complications are rare. Endoscopic treatment entails greater patient convenience, lower morbidity (e.g., pain, abdominal scar), and reduced cost [43, 44]. Consequently, a significant parental preference for endoscopic treatment is evident [10, 11]. A recent study demonstrated that both, patients and parents viewed injection therapy as the least bothersome aspect of VUR treatment followed by antibiotic prophylaxis and VCUG [8].

Table 1: Success rates of endoscopic treatment for primary VUR. Meta-analysis by Elder JS et al. 2006 summarizes results until 2003. More recent series are listed below. Initial success after one treatment and final success after two or more treatments.

Reference	Bulking agent	Injected volume	Ureters	Follow-up	Success	
					Initial	Final
Elder et al. 2006 [27]	Various	0.2–1.7 mL	8101	variable	76%	85%
Capozza et al. 2004 [33]	Various	0.2–2.2 mL	1694	12–204 months		77%
Kirsch et al. 2004 [5]	Dx/HA	0.5–1.5 mL	119	3–12 months	92%	
Kirsch et al. 2006 [34]	Dx/HA	0.8–2.0 mL	139	3–18 months	93%	
Van Capelle et al. 2004 [35]	PDMS	0.2–2 mL	311	3–110 months		75%
Kajbafzadeh et al. 2006 [36]	Ca hydroxylapatite	0.4–0.6 mL	364	6 months		69%
Yu and Roth 2006 [6]	Dx/HA	1 mL	162	2–26 months	87%	93%
Puri et al. 2006 [37]	Dx/HA	0.2–1.5 mL	1101	3–46 months	87%	96%
Lorenzo et al. 2006 [38]	PDMS		351	72 months		72%
Pinto et al. 2006 [39]	Dx/HA		86	3 months		84%

Table 2: Success rates of endoscopic treatment for complex VUR.

Reference	Pathology	Bulking agent	Injected volume	Ureters	Follow-Up	Success
Perez-Brayfield et al. 2004 [13]	Neurogenic bladder	Dx/HA	0.4–2.0 (1.1)	9	3 months	78%
Capozza et al. 2002 [25]	Voiding dysfunction	Dx/HA			3–6 months	49%
Elmore et al. 2006 [26]	Failed initial injection	Dx/HA	1.0–1.5	53	3 months	89%
Perez-Brayfield et al. 2004 [13]	Failed reimplantation	Dx/HA	0.4–2.0 (1.1)	19	3 months	88%
Kitchens et al. 2006 [14]	Failed reimplantation	Dx/HA	0.7–3.8 (0.8)	20	19 months	83%
Campbell et al. 2006 [29]	Renal transplantation	Dx/HA		11		55%
Molitierno et al. 2007 [30]	Duplicated ureter	Dx/HA	0.8–2.8 (1.4)	63	1–3 months	85%
Cerwinka et al. 2007 [31]	Paraureteral diverticulum	Dx/HA	0.8–1.8 (1.2)	20	6.6 months	81%
Chertin et al. 2007 [32]	Ureterocele	Various		44	1–21 months	91%

3.3. Complications

The most common complications following endoscopic treatment of VUR are new contralateral VUR (2.3–17.3%) and treatment failure [35, 38]. Less than 4% of children complain of flank pain or emesis several hours after the procedure and all respond to analgesics [5]. Gross hematuria, urinary retention, or febrile UTIs have not been observed. The most significant potential complication of endoscopic treatment for VUR includes a 0.6% risk of ureteral obstruction [45]. Our obstruction rate is 4 ureters (2 patients) in over 1200 ureteral injections, or <0.3%. A 7-month old boy with bilateral grade V VUR and spina bifida developed acute renal failure and had bilateral ureteral stents placed. A STING technique using 0.7 mL was utilized. A postoperative VCUG after stent removal showed bilateral grade V VUR and a vesicostomy was performed. Interestingly, no VUR was seen at the time of bladder augmentation 5 years later. A 6-year old girl developed bilateral ureteral obstruction after HIT using 1.1 mL and 0.7 mL. Bilateral nephrostomy tubes were placed and removed 6 weeks later after a normal antegrade study. The VCUG did not show any evidence of VUR and no further treatment was required.

Factors that may increase the risk of obstruction include bladder dysfunction and markedly dilated ureters. Patients with recurrent VUR often remain asymptomatic and without risk factors for pyelonephritis such as young age, voiding dysfunction, or significant history of UTIs may be taken off antibiotic prophylaxis [46]. Febrile UTIs after radiographically successful endoscopic treatment warrant evaluation for recurrent VUR.

3.4. Potential future applications

As endoscopic treatment continues to be applied to more complex cases of VUR and outcome data become available, the indication for endoscopic treatment may exceed the scope of primary VUR. In the USA, for example, duplex ureters are no longer considered a contraindication for endoscopic treatment with Deflux by the FDA. Outcome analysis of complex cases of VUR will aid in preoperative counseling and patient selection and paired with proper technique further improve success rates of endoscopic VUR treatment. As adults with recurrent pyelonephritis are more consistently evaluated for VUR, a patient population with distinct requirements and disease characteristics may

Table 3: Variables affecting the outcome of endoscopic treatment of VUR with Deflux. Overall success for patients/ureters.

Reference	Bulking agent	Patients/Ureters	Mean age	Overall success	Predictors of success	Not predictive
Lavelle et al. 2005 [40]	Dx/HA	52/80	7.6 years	71%/80%	Volcano: present 87% absent 53%	Voiding dysfunction VUR grade Injected volume
Yucel et al. 2007 [41]	Dx/HA	168/259	4.2 years	82%/86%	Volcano: present 87% absent 36% Volume: <0.5 mL success >0.5 mL failure VUR grade	Voiding dysfunction Laterality
Routh et al. 2007 [42]	Dx/HA	301/453	5.5 years	66%/72%	VUR grade Surgeon	

emerge. Finally, once more accurate predictors of VUR resolution/persistence become available, endoscopic treatment may be more frequently used as the primary treatment in patients with low probability of VUR resolution.

4. CONCLUSIONS

Endoscopic treatment of VUR offers significant advantages to patients and avoids potentially complicated open surgery. While success of endoscopic treatment for primary VUR approaches that of ureteral reimplantation, it is acceptable in complex cases of VUR. Consequently, endoscopic injection has assumed the role of first-line VUR treatment whereas ureteral reimplantation remains reserved for cases of failed injection therapy or significant anatomical abnormalities. The development of new injectable agents in combination with the improvement of endoscopic techniques will continue to strengthen the role of endoscopic treatment for VUR.

ABBREVIATIONS

VUR: Vesicoureteral reflux
UTI: Urinary tract infection
STING: Subureteric Teflon injection
VCUG: Voiding cystourethrography
FDA: Food and Drug Administration
HIT: Hydrodistention Implantation Technique
HD: Hydrodistention
UO: Ureteral orifice.

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Review Article

A Review of the Effect of Injected Dextranomer/Hyaluronic Acid Copolymer Volume on Reflux Correction Following Endoscopic Injection

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The current literature suggests that multiple variables affect vesicoureteric reflux (VUR) resolution rates following dextranomer/hyaluronic acid copolymer (Dx/HA) injection. This article reviews the evidence pertaining to the effect of injected Dx/HA volume on success rates following endoscopic correction. Lack of prospective studies which use injected volume as a continuous variable coupled with a nonstandardized injection technique and endpoint hinders the ability to reach a definite conclusion.

1. INTRODUCTION

The approval of dextranomer hyaluronic acid copolymer (Dx/HA) by the FDA in 2001, coupled with its safety and ease of injection, has led to a rapid increase in its use for treating vesicoureteral reflux (VUR) [1]. This has been accompanied by a reevaluation of the treatment philosophy for VUR, promulgated by both a change in physician preference and driven by parents who are opting for endoscopic correction over long-term follow up and antibiotic prophylaxis [2, 3]. However, in the era where basic concepts about VUR and its role in UTI and renal scarring continue to evolve, the mere availability of a minimally invasive approach cannot, in of itself, immediately justify the adoption of changed indications for VUR correction. Moreover, despite the high success rates shown in some large series, endoscopic VUR correction using Dx/HA has not yet achieved the success rates following open surgery [4]. It is, therefore, imperative that factors associated with success following Dx/HA injection are identified in order to improve surgical outcomes, gain insight into potential mechanisms which underlie success as well as failure, and enable better patient selection and preoperative counseling (Table 1).

The current paper reviews the impact of injected Dx/HA volume on primary VUR correction rates. Studies analyzing this variable are discussed along with the findings of a recent multivariable analysis conducted at our institution.

2. EFFECT OF INJECTION TECHNIQUE ON THE VOLUME OF Dx/HA

The known principles for VUR correction are derived from dissections dating back to the description of the physiologic submucosal tunnel by Paquin in 1950s, which defined the mechanistic basis of open surgical procedures to correct VUR [5]. By extrapolation, the goal of endoscopic injection is to create an effective valvular surrogate by providing submucosal support for the entire length of whatever portion of the refluxing ureter, that is, transvesical. This is achieved by accurate injection of sufficient amount of the bulking agent in a correct plane. The hydrodistension implantation technique (HIT) popularized by Kirsch and subsequently modified to a double HIT procedure has highlighted the importance of hydrodistension in enabling an intraureteric injection to target support to the entire intravesical ureter [6]. This technique was based on the initial description by Chertin et al. for injection therapy in children with high-grade VUR [7]. As opposed to the classical STING (subtrigonal injection) technique, which aims at achieving a good mound at the ureteral orifice, the HIT tends to

involve higher volumes of injection as it aims to support the entire ureteric length. Moreover, obliteration of any further hydrodistension of the ureteral orifice is the endpoint in this technique rather than a good mound. Clearly, establishing this endpoint may further lead to higher injection volumes. Therefore, reported volumes of injection in all studies should be interpreted with caution, and both technique and volume should be studied as distinct variables in a multivariable analysis.

3. EFFECT OF INJECTED Dx/HA VOLUME ON OUTCOME

The mean injected volume of Dx/HA injected in all series reported to date varies between 0.2 mL to >1 mL [2, 3, 6, 8–16]. The impact of injected volume on success is variable (Table 2). Kirsch et al. found no statistical difference in injected volume between successes and failures using a mean of 0.83 mL in 459 ureters [8]. In a follow up study using a mean volume of 0.9 mL, the same authors demonstrated a positive impact of increasing experience as well as injected volume, with improved success rates from 60 to 74% [6]. The third variable, which then prompted a further improvement in the success rate to 89%, was the use of the "modified STING" or HIT. The HIT technique involves placing the needle into the mid to distal ureteral tunnel itself at the 6-o' clock position and watching the entire tunnel coapt as the injection progresses. In contrast, the traditional STING technique, judged by both the mechanism and endpoint of injection (a mound at the ureteral orifice alone, not involving the intravesical ureter, and in effect creating a surrogate nipple valve rather than flap valve mechanism at the ureteral orifice to prevent VUR) would presumably require a relatively lesser injected volume. Though not highlighted in the paper, the injected volumes were indeed higher in this subset of patients (1–1.5 mL), compared to the STING group.

In contrast, in two subsequent studies where mean injected volumes of Dx/HA were ≥0.8 mL, no correlation with VUR correction was noted [9, 10]. Lavelle et al. reported that the average injected volume was 0.84 mL in those with successful VUR correction when compared with 0.94 mL in failures (p = NS) [9]. Mound morphology was the only statistically significant predictor of success; 87% of ureters that showed a "volcano" configuration were corrected as opposed to only 53% in those with an "alternate" morphology. Although Routh et al. did not demonstrate an effect of injected volume in their study, the authors acknowledged that their injection volume had increased over time based on the positive experience of other authors [10].

Yucel et al. performed a multivariable analysis of their experience with Dx/HA injection and showed that an injected volume of <0.5 mL was significantly associated with success as compared to a volume >0.5 mL [11]. The overall reflux correction was 70% by patients and 78% by ureters (mean VUR grade 2.6) as compared to 89% and 92%, respectively (mean VUR grade 2.6), in the study by Kirsch et al. [6]. Similar to the findings of Lavelle et al., this study showed that mound morphology was the most important indicator of VUR correction. The authors speculated that a higher volume of Dx/HA implied a technically more difficult injection resulting in a poorer outcome. No evidence was provided to support this conjecture. Moreover, it is unlikely that all injections in the HIT series by Kirsch et al. were uniformly more difficult to alone account for greater injected volumes. As stated above, a priori performance of a double HIT injection is likely to require more injected material. Alternatively, the findings of Yucel et al. may reflect that the analysis was based on a cutoff close to their mean injected volume, rather than treating the injected volume as a continuous variable.

Another multivariable analysis published in 2007 attempted to look at the effect of volume using a 1 mL cutoff. Routh et al. treated 301 patients (453 ureters) with VUR using an average 0.93 mL Dx/HA with a 75.5% success rate by ureters [12]. The authors noted that preoperative VUR grade and the operating surgeon were significant predictors of outcome. The technique of injection (HIT versus STING) was significant on a univariate analysis but only showed a trend toward significance for HIT on a multivariable analysis (P = .056). However, with respect to volume, no difference in success rates was noted when injected Dx/HA volume was analyzed as a cutoff of <1 mL or >1 mL. It is possible that arbitrarily choosing a 1 mL cutoff volume may have missed an actual significant cutoff volume, thereby, failing to detect any volume effect. Moreover, as rightly pointed out by the authors, there is also a possibility that the positive effect of higher volume is nullified by the fact that higher volumes are more likely to be used for higher grades of VUR.

We performed a retrospective review of 126 consecutive patients with primary VUR (196 refluxing ureters) who underwent injection for febrile urinary tract infections (UTI) to identify factors associated with success following Dx/HA injection [13]. Endoscopic injection was performed using both the STING and the HIT techniques in this series though neither were prospectively planned in any patient nor systematically varied over the course of the series. Success was defined as resolution of VUR after first injection on post-operative VCUG performed 3 months following endoscopic treatment. Univariate and multivariate regression analysis were performed on the following variables: age at surgery, gender, laterality, time between presentation and surgery, preoperative VUR grade, surgeon experience, lower urinary tract symptoms (LUTS), and volume of Dx/HA injection. Statistical analysis was performed with SPSS version 13.0 software (SPSS Inc., Chicago, Ill, USA), with P-values less than .05 considered statistically significant.

By renal unit, VUR grades were as follows: I in 7(3.5%), II in 53(27%), III in 91(46.4%), IV in 30(15.3%), and V in 15(7.6%), with a mean VUR grade of 3. Success rate after 1 injection was 50% by patient and 59.2% by ureter. Success rate by grade was 100% for grade I, 75% for grade II, 57% for grade III, 37% for grade IV, and 46% for grade V. Mean injected volume was 0.9 ± 0.27 mL in those who had a successful injection versus 0.67 ± 0.24 mL in those who failed (P < .001). Success after 1 injection was 78.9% using ≥0.8 mL Dx/HA compared to 31.7% with <0.8 mL. The mean Dx/HA volume increased from 0.75 ± 0.26 mL in

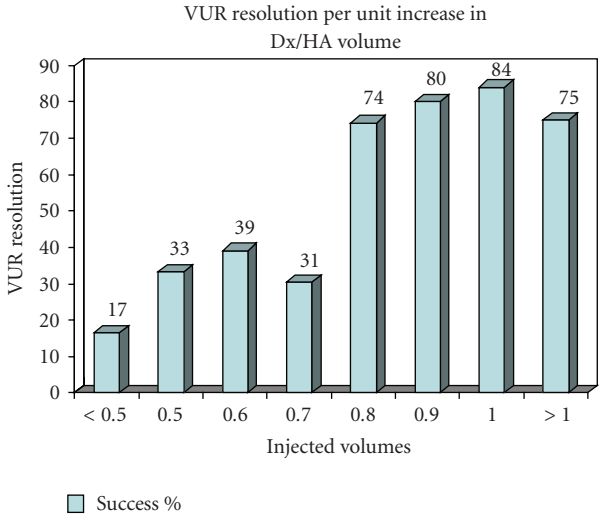

Figure 1: VUR correction rates for each 0.1 mL increment in injected Dx/HA volume.

Table 1: Reported variables associated with VUR correction using Dx/HA.

Variables associated with VUR correction following Dx/HA injection
(1) Mound morphology
(2) Grade of VUR
(3) Surgeon experience/learning curve
(4) Injection technique
(5) Volume of Dx/HA
(6) Absence of ureteric dilatation
(7) Location of ureteral orifice (degree of lateral ectopia)
(8) Age of patient
(9) Resident participation
(10) Fewer needle insertions
(11) Absence or correction of lower urinary tract symptoms

the first 98 ureters treated to 0.87 ± 0.29 mL in the last 98 ($P = .002$), a change that was associated with a simultaneous improvement in the success rate for grade III VUR from 50 to 68%. This increase in injected volume was not prompted by an interim assessment of our results, though it can be speculated that it may be a reflection of a change in technique form the classical STING to the HIT (see above). However, there was no statistical difference in the mean injected volume for high- and low-grade VUR: I–II (0.82 ± 0.29 mL) versus III–IV (0.78 ± 0.26 mL), indicating that grade did not influence injection volume across the series. The success rates for each 0.1 mL increase in injected Dx/HA volume is plotted in Figure 1. Our analysis showed that for each 0.1 mL increment in the injected Dx/HA volume, a statistically significant improvement in success rate was observed when compared to correction achieved below that cutoff volume. This volume effect persisted up to a maximum of 1 mL injected beyond which no further increase in success rate was observed (see discussion of arbitrary choice of cutoff volume in [12] above). Multivariable analysis confirmed that higher Dx/HA volume ($P = .001$), lower preoperative grade ($P = .013$), surgeon experience ($P = .025$), and treatment of LUTS ($P = .009$) were all independently associated with successful correction of VUR.

4. CAN INJECTED VOLUME IN ASSOCIATION WITH OBLITERATION OF HYDRODISTENSION BE USED IN COMBINATION TO PREDICT SUCCESS?

The use of mound morphology as the injection progresses as a predictor of VUR resolution is fraught with some inherent drawbacks. What defines a "good" mound is a subjective measure much like the subjectivity of the "good urethral plate" in hypospadias surgery; both are qualitative, difficult to define, and are based on surgeon experience. Secondly, the mound is a 2-dimensional view of the effect of the injection at the ureteric orifice, but gives no indication of the support achieved, if any, along the entire intra vesical ureter. In addition, the mound at injection may not be the mound at the time of reassessment by a VCUG at 3 months. There is a well-documented 19% decrease in the injected Dx/HA bolus over 3 months [8]. This volume reduction occurs because the dextranomer microspheres constitute 50% of the volume in Dx/HA and their hydrolysis overtime will alter the mound morphology, likely shrinking it somewhat, notwithstanding the stabilizing effect of collagen ingrowth [17]. This coupled with a risk of bolus migration would mean that the surgeon could use mound morphology as a predictor of VUR correction *at the time of injection* but this endpoint may not be a stable indicator of longer term success. In studies which showed the effect of a "favorable" mound morphology on outcome, VUR resolved in 53% of ureters in Lavelle's series and in 36% in the study by Yucel et al. [11]. Moreover, up to 12% of "good" mounds can have persistent VUR following Dx/HA injection [18].

These studies all share the inherent limitations of nonrandomized retrospective reviews. In the present paper, this primarily involves failure to identify and include of all confounding variables which could impact the results. For example, one of the criticisms of our study is that the technique of injection (HIT versus STING) was not analyzed. Moreover, the very indications for treatment of the reflux vary from study to study, along with the severity of VUR further confounding the results and their comparison with other studies.

5. CONCLUSIONS

There are several factors which may predict successful VUR correction following Dx/HA injection. Our study revealed the presence of a direct association between injected volume and VUR correction, by treating volume as a continuous variable, even while controlling for other variables, highlighting its importance as a true success modifier. The injected volume of Dx/HA is a factor, which to a degree under the direct control of the surgeon. Given the exigencies of materials cost, and the expectation on surgeons

Table 2: Studies investigating the effect of injected Dx/HA volume on VUR correction.

Series	Refluxing units; mean Dx/HA volume (mL)	Mean grade	Volume injected (mL) success/failures	Method of statistical analysis	Success by grade (%)	Effect of volume of injected Dx/HA
Kirsch 2003	292 0.83 ± 0.03	2.6	S: 0.9 ± 0.3 F: 0.9 ± 0.2	Univariate	I 90; II 82; III 73; IV 65	NS
Kirsch 2004 modified STING	119 >0.9	2.8	S: 1.0 F: 1.5	Univariate	I 100; II 90; III 91; IV 89	Higher volume significant
Lavelle 2005	80 NA	NA	S: 0.8 F: 0.9	Univariate	I 82; II 84; III 77; IV 73	NS
Routh 2006	225 pts 0.8 (0.3–2.0)	2.4	S: 0.8 (0.4–2.0) F: 0.8 (0.3–1.8)	Univariate	I 63; II 72; III 57; IV 14 (By patients)	NS
Yucel 2007	259 0.54 ± 0.2	2.6	NA	Studied as categorical variable with cutoff </>0.5 mL using multivariable analysis	I 100; II 83; III 73; IV 53, V 29	Lower (<0.5) volume significant
Routh 2007	453 0.93 (0.2–3.5)	2.3	NA	Studied as categorical variable with cut off </>1 mL using multivariable analysis	I 83; II 82; III 66; IV 53	NS
Dave 2007 (Accepted J Urol)	196 0.8 ± 0.03	3	S: 0.9 ± 0.2 F: 0.6 ± 0.2	Studied as continuous variable using multivariable analysis	I 100, II 75; III 57; IV 37; V 46	Higher volume significant on multivariable analysis

to use available medical resources responsibly, without a clear demonstration of the effect of volume on results, the surgeon is to a certain extent hesitant to use only a small portion of a second Dx/HA syringe, beyond the 0.8–1 mL available for injection in the standard commercially available syringe. Based on our experience, we now adopt a more aggressive approach in injecting a minimum of 0.8 mL irrespective of the grade of VUR and ensure obliteration of hydrodistension at the end of injection. From a cost stand point, an injection failure definitely involves higher costs and, therefore, it is reasonable to use a higher volume at the initial attempt to improve success rates. Syringes with slightly greater volumes of 1.2–1.4 mL, should they become available in the future, may provide greater treatment flexibility in this regard. Finally, though endoscopic injection for VUR is generally accepted as a simple procedure, the importance of technique and experience are evident in most studies. Further prospective studies which include all variables, and which possibly perform hydrodistension in a standardized manner, need to be conducted to identify factors which can be used for patient counselling, and increase success rates to those won by open correction of VUR.

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Review Article

Has the Data Efflux Regarding the Promising Outcome Following Injection of Deflux Changed the Management of Adult Vesicoureteral Reflux?

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Primary vesicoureteral reflux (VUR), traditionally considered a problem of childhood, can also be detected during adulthood. However, while the concept regarding the therapeutic management of VUR in children has undergone revolutionary changes, moving from surgical to conservative approach, the optimal therapeutic approach in adult reflux is poorly addressed and is still unknown. Herein, we review clinical and therapeutic approaches of VUR in pediatric population as published throughout the years. With the introduction of Deflux injection as a minimally invasive procedure, we identify a beginning of a new trend that further extends the indications for endoscopic injections, including its introduction to adult patients as well.

1. INTRODUCTION

Primary vesicoureteral reflux (VUR), traditionally considered a problem of childhood, can also be detected during adulthood [1]. However, while the concept regarding the therapeutic management of VUR in children has undergone revolutionary changes, moving from surgical to conservative approach, based upon solid prospective data, the optimal therapeutic approach in adult reflux is poorly addressed in the literature and is still unknown. The current therapeutic strategy for management of reflux has drawn its inspiration from three important large prospective studies dealing with the management of VUR [2–4]. The most comprehensive was the International Reflux Study (IRS), where 452 patients in Europe and USA were randomly allocated to medical and surgical arms. In 5 years follow-up, the same incidence of urinary tract infection (UTI) was seen in both arms (38%), though surgery was more effective in preventing pyelonephritis (PN) (21% versus 10%). However, in 10 years follow-up, clinical findings did not support the surgical attitude as there was no significant difference in renal growth comparing both arms, and there was no support to the view that the outcome of renal function is improved by surgical correction of VUR in children with bilateral disease. These studies had led to the publication of the clinical guidelines for the management of VUR in children, both by the American Urological Association (AUA) [5] and the European Association of Urology (EAU) [6].

In general, conservative attitude is currently the mainstay, and surgical intervention takes its place in the more severe conditions. While those observations are extremly important in children, they are irrelevant for adults as factors such as the natural history of the disease, the associated risks such as infections or scars are completely different. Unfortunately, with regard to VUR in adults, review of the literature reveals only few retrospective studies, some of them biased with conflicting results.

2. PREVALENCE OF VUR IN ADULTS

In the general pediatric population, the prevalence of VUR is around 1-2% with higher rates in siblings (30%) and in children with acute PN (25–40%) [5].

As the rates of disappearance of VUR in children are as high as 71% and can occur at any age, in infancy or at puberty [7], the actual prevalence in adults is still unclear. Baker and coworkers [8] found an incidence of 26.4% of VUR in

children but only 5.2% in adults, each group suspected of "having infravesical obstruction".

Similarly, Choi et al. [9] studied 86 adult women suffering from uncomplicated PN with voiding cystourethrogram (VCUG) performed on the 3rd and the 7th days of antibiotic treatment, and only in 2 cases (2.3%), VUR was demonstrated.

Pinthus et al. [10] explored the same situation in 47 women who presented with acute PN. Early indirect cystography revealed VUR in 28%, while VCUG performed later found VUR in only 3 patients (9%). In accordance, while the resolution rates of reflux in children are rather predicted, it seems that the possibility of resolution even past puberty still exists, yet the chance for resolution is probably much less than in infants [11].

3. PRESENTATION

The most common initial symptoms and findings that can lead to the diagnosis of VUR are UTI, asymptomatic bacteriuria, proteinuria, renal failure, and hypertension [12]. Köhler et al. followed after 115 adult patients and found UTIs in 87%, hypertension in 34%, renal calculi in 18%, and back pain in 42% [12]. Vice versa, reflux nephropathy may be clinically latent as the prevalence of reflux in patients with incidentally diagnosed adult hypertension exceeds to 19%, without any apparent renal parenchymal or renovascular involvement [13]. However, the correlation between presence of VUR and various clinical presentations cannot be made that easily as different, and somehow confounding observations were published in other studies and in some patients the reflux may be even completely asymptomatic [11].

4. THE CURRENT APPROACH FOR MANAGEMENT OF ADULT VUR

So far, although no evidence-based recommendations are available in the literature, the last AUA update (1998) [11] for the treatment of VUR in adolescents and adults recommends the following.

(i) No medical management is needed in VUR grade 1-2 and no history of UTI.

(ii) Medical management with lifelong antibacterial prophylaxis should be considered in the cases of low-grade VUR, shortened life expectancy, and poor surgical risk.

(iii) Surgery is indicated in VUR grade 3 or higher, history of recurrent PN, and evidence of nephron loss.

When conservative treatment is the mainstay, progressive renal damage and caliceal scarring should be expected [14]. Reimplantation, when performed, does not improve hypertension or renal failure, but it rather stops the anticipated progressive deterioration [10, 15].

Similar conclusions were coming up from Köhler and Guthman's studies [16, 17]. In the first study [16], surgical treatment (e.g., ureteral reimplantation) did not alter the frequency of lower UTI, though it significantly decreased the frequency of PN. Yet, the surgical option according to the author should be considered only when conservative treatment failed and not with the aim of arresting renal functional deterioration. However, the second study [17] had expanded the indications for surgical treatment also for asymptomatic women in childbearing age "in whom pyelonephritis of pregnancy would pose a major risk to the fetus and mother", without supporting evidences. Ever since, most clinicians recommend that surgical correction of VUR should be accomplished before pregnancy in women at childbearing age or even earlier in girls with reflux that persists beyond puberty.

This recommendation is based upon the fact that history of VUR is known to increase morbidity during pregnancy including the risk of preeclampsia, obstetric interventions, and fetal loss. Women with hypertension and an element of renal failure are particularly at risk, though surgical correction does not prevent complications but rather decreases their frequency [18]. It should be also remembered that reimplantation in adults is more difficult with lower success rates compared to infants. This can be attributed to difficult bladder exposition, increased vascularity around the ureter and in the retrovesical space, and increased body mass [11].

Altogether, VUR in adults is still a very controversial subject, and throughout the years, the pendulum had moved from surgical to a more conservative treatment and again to surgical treatment in certain and severe cases.

5. ENDOSCOPIC CORRECTION OF VUR

During the last seven years, we are witnessing an increasing number of studies published in the English literature, discussing the safety and efficacy of endoscopic injection of bulking materials for the correction of ureteric reflux. The need for alternative treatment aroused as a result of the significant disadvantages of both reimplantation and antibiotic prophylaxis. Reimplantation in the pediatric population carries significant cost, morbidity, and inpatient hospital stay, while antibiotic prophylaxis requires annual imaging which is expensive, invasive, and often requires sedation [19].

The first report on endoscopic injection of polytetrafluoroethylene (Teflon) in pigs came from Puri and O'Donnell in 1984 [20]. Later on, long-term results were published covering 8332 children and 12251 refluxing ureters [21], and the final conclusion was that "polytetrafluoroethylene injection is a simple, safe and effective outpatient procedure for treating all grades of vesicoureteral reflux." Chertin and Puri [22] supported their own conclusion by reporting long-term (e.g., six years) follow-up among 258 patients with primary VUR who were treated by polytetrafluoroethylene injection. They reported overall success rates of 77% following one injection, 13.5% success rate following two injections, 2.6% following three injections, and 0.5% following four injections. Yet, the initial enthusiasm from PTFE has disappeared following the observation that small particles can be injected directly into capillaries and embolize to distant organs, causing the FDA to withdraw PTFE

from the United States market [23]. Remaining with the impressive results of the endoscopic injection for treating vesicoureteric reflux, alternative materials took the PTFE place in order to keep its momentum of success, while keeping complication rates as low as possible. At present, the most popular injectable material is dextranomer/hyaluronic acid (Dx/HA) copolymer (Deflux) which is FDA approved. This is an organic substance comprising 80–250 μm microspheres which are nonallergic, nonimmunogenic, and have no potential for malignant transformation [24, 25]. The large size of the microspheres prevents them from migrating outside the urinary bladder and they do not tend to form granulomas or induce calcifications [24].

Injection procedure consists of injecting the bulking material through direct inspection and under general anesthesia. Approximately, 1 mL of Deflux is submucosally injected through a special needle, which is inserted 2-3 mm below the affected ureteral orifice at the 6 o'clock position [25, 26]. The needle is slowly withdrawn as a "volcanic bulge" starts to create [25]. Overall procedure length does not exceed 30 minutes [26, 27], and the patient is discharged home the same day [19, 23, 27, 28] or the following day [24].

Overall complication rate is very low, and the procedure is considered very safe and effective. UTI, flank pain, postoperative ureteral obstruction, retrograde tracking of Deflux, intravesical extravasation of Deflux, and new contralateral VUR were reported in only few percents (0.6–4.5%) [23, 28, 29].

Success rates, on the other hand, are high and reported in various series with regard to the number of injections required to cure VUR and to the original reflux grade. Following a single injection, the reported success rates in pediatric population vary between 72–86%, following two injections—between 12-13% and following three injections—between 1-2% [23, 25, 27, 28]. Overall, cure rates reached 82–100% for grade 1 reflux, 82–88% for grade 2, 73–87% for grade 3, 64–73% for grade 4, and 50% for grade 5 [19, 23, 28]. Kirsch et al. [23] describe the lowest success rates (60%) in the first twenty cases, meaning that a reasonable learning curve exists for this certain procedure.

6. THE EVOLVEMENT OF THE THERAPEUTIC APPROACH IN ADULTS

All the advantages mentioned with regard to endoscopic treatment for VUR in children can definitely change the concept regarding the treatment of VUR in adults. Arguments such as high success rates, very short hospital stay, absence of significant postoperative complications, safety of injectable materials, and low cost compared to the cost of long-term antibiotic prophylactic treatment which have been raised in discussions regarding children [30–32], are also valid concerning adults. Understandably, this can widen the circle of patients treated with bulking agents to include also adults. However, in oppose to increasing reports regarding using this technique in the pediatric age group, the reported experience in adults with Deflux is very limited [19, 29, 33]. Those reports usually describe the outcome of injection of various substances in series composed of mixed populations, including children and adults. Although there is usually no specific reference to the adult subgroup, it is obvious that there has been some experience with injection of cross-linked bovine collagen [34] or STING [35, 36] in adults, with cure rates as high as 86% following the injection of polymethylsiloxan in adult women or 70% following the first injection of Teflon in adults [36].

Nowadays, in the "Deflux era", review of the literature as well as presentations in urological conferences can identify the beginning of a new trend that further extends the indications for endoscopic injections, including its introduction to adult patients as well. Some current pediatric reports [19, 29] include in their series some adult patients as old as 22 years. Unfortunately, they do not specify this unique population in terms of number of individuals, sex, indications for Deflux injection, age at injection, follow-up length, complications, and success rates. However, we can assume that both groups were stunned by their impressive success rates, and taking into consideration that endoscopic treatment for VUR is "self and efficacious with low-complication rate" [19], they decided to offer it to certain individuals that traditionally were excluded from any definitive treatment. Enthusiasm from the introduction of Deflux injection for adult population was also expressed by Kirsch [37] who achieved success rates of 90 and 95% after one or two treatments in 22 patients ranging in age between 13–71 years.

In summary, the efflux of data regarding the safety and the promising results of Deflux endoscopic correction of VUR in children will certainly change the management of VUR in adults which unfortunately has been poorly addressed and controversial till recently. In similar with the shifting therapeutic policy of adult ureteropelvic junction obstruction following the arrival of the endourological era [38], one can likewise anticipate that "it would be unethical to refrain from treating" [30] adult patients diagnosed with VUR. Furthermore, as the procedure is safe, less invasive, highly successful, and can be repeated, we foresee that a more active strategy, namely, early endoscopic correction, will become the new gold standard of treatment of adult VUR, and we hope that this shift of policy will be clearly reflected in the coming updated clinical urological guidelines for management of VUR.

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Review Article

Current Status of Gil-Vernet Trigonoplasty Technique

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Significant controversy exists regarding vesicoureteral reflux (VUR) management, due to lack of sufficient prospective studies. The rationale for surgical management is that VUR can cause recurrent episodes of pyelonephritis and long-term renal damage. Several surgical techniques have been introduced during the past decades. Open anti-reflux operations have high success rate, exceeding 95%, and long durability. The goal of this article is to review the Gil-Vernet trigonoplasty technique, which is a simple and highly successful technique but has not gained the attention it deserves. The mainstay of this technique is approximation of medial aspects of ureteral orifices to midline by one mattress suture. A unique advantage of Gil-Vernet trigonoplasty is its bilateral nature, which results in prevention from contralateral new reflux. Regarding not altering the normal course of the ureter in Gil-Vernet procedure, later catheterization of and retrograde access to the ureter can be performed normally. There is no report of ureterovesical junction obstruction following Gil-Vernet procedure. Gil-Vernet trigonoplasty can be performed without inserting a bladder catheter and drain on an outpatient setting. Several exclusive advantages of Gil-Vernet trigonoplasty make it necessary to reconsider the technique role in VUR management.

1. INTRODUCTION

Vesicoureteral reflux (VUR) is the most common urologic anomaly in children, affecting almost 1% of normal children [1, 2]. VUR is most commonly diagnosed during investigation of a child with history of urinary tract infection (UTI) [3, 4]. The frequency of VUR in children with UTI is 20–40% [5]. Evidence of renal involvement following UTI is more commonly found in children with VUR than children without VUR [6]. The combination of VUR and UTI predisposes children to acute pyelonephritis (APN) [7, 8]. Annual cost of hospitalization for pyelonephritis exceeds $180 000 000 in the U.S [9]. APN leads to subsequent renal scarring in 15–52% of the affected children [10, 11]. Renal scarring is an important risk factor for end stage renal disease (ESRD) and hypertension [2, 12]. ESRD is associated with reflux nephropathy in 3–25% of children and 10–15% of adults [5, 13].

Cooper and Austin have considered VUR as the "prostate cancer" of pediatric urology [14]. Significant controversy exists regarding VUR management, due to lack of sufficient prospective studies. The primary goal of VUR management is to prevent kidney damage. Management options include conservative medical treatment (antibiotic prophylaxis), and surgery (open or endoscopic). There are two important unanswered questions on who is a suitable candidate for antireflux surgery, either open or endoscopic, and which technique is the best for a patient. VUR resolves spontaneously with time in a large proportion of patients. Spontaneous resolution rate of VUR depends on reflux severity and patient's age at diagnosis, with higher rates at lower stages and younger ages. Reflux resolves in about 80%, 50%, and 30% of cases with VUR grades I to II, III, and IV, respectively [15–17]. The rationale for medical management is based on the potential of VUR for spontaneous resolution or decrease in severity, and on the ability of antibiotics to prevent UTIs and minimize renal damage until VUR ceases. Medical and surgical treatments of VUR have been compared in a meta-analysis, the results indicate that there is no significant difference in renal growth or scarring, and recurrence of UTI but the incidence of pyelonephritis is significantly reduced in surgical group [18]. The need for long-term daily medication, potential side effects, incompliance to the dosing regimen, and need for taking several voiding cystograms are disadvantages of medical management of VUR [19, 20]. The rationale for surgical management is

that VUR can cause recurrent episodes of pyelonephritis and long-term renal damage. Despite controversies regarding indications of surgical treatment, expert opinion panels have described their recommendations on who is a good candidate for surgery. The AUA Pediatric Vesicoureteral Reflux Guidelines Panel recommended medical treatment as the initial management for all children with VUR diagnosed following UTI, with the exception of children over 1 year of age with grade V and older children with bilateral grade IV VUR. Indications for antireflux surgery include failure of renal growth, febrile UTI despite prophylaxis, noncompliance with medical management, the presence of new scars or deterioration of renal function, and reflux associated with congenital abnormalities of the ureterovesical junction [21]. Recommended indications are mostly based on expert opinions rather than on prospective controlled trials. To decide whether surgery is indicated for a particular child, the benefits and risks of surgical and medical management must be carefully assessed and individualized. In addition to the published indications for antireflux surgery, some other factors such as renal function, bladder function, and parental preference affect the final decision on selection of management options [22–24].

Antireflux surgical procedure may be performed endoscopically or open. The first report on antireflux surgery was published by Hutch in 1952 [25]. Several surgical techniques have been introduced during the past decades. Open antireflux operations have high success rate, exceeding 95%, and long durability. However, these techniques are invasive and impose a risk, although small, of surgical complications to the patient. Open techniques are categorized in two main groups; intravesical and extravesical. Politano and Leadbetter described an intravesical antireflux operation using ureteroneocystostomy in 1958 [26]. Other intravesical operations include ureteral advancement techniques; trigonal (Glenn-Anderson), (2) cross-trigonal (Cohen), and (3) medial advancement (Gil-Vernet). Extravesical ureteral reimplant was introduced by Lich and Gregoir in 1961 [27, 28].

In the era of minimally invasive surgery, particularly for procedures with high success rate, capability of a technique to minimize surgery associated morbidities is significantly focused by most surgeons. The purpose of this article is to review the Gil-Vernet antireflux operation. Unfortunately, this simple and highly successful technique [29–31] has not gained the attention it deserves in urology field; it has not been evaluated by experts thoroughly. Since the technique was introduced by Gil-Vernet, the author and his colleagues have used this technique in more than one thousand pediatric and adult patients in their center, and published the results in several reports [32–34] (Figure 1). This article recalls the advantages of Gil-Vernet technique such as high success rate, being simple and rapid, and its potential to be performed on an outpatient setting.

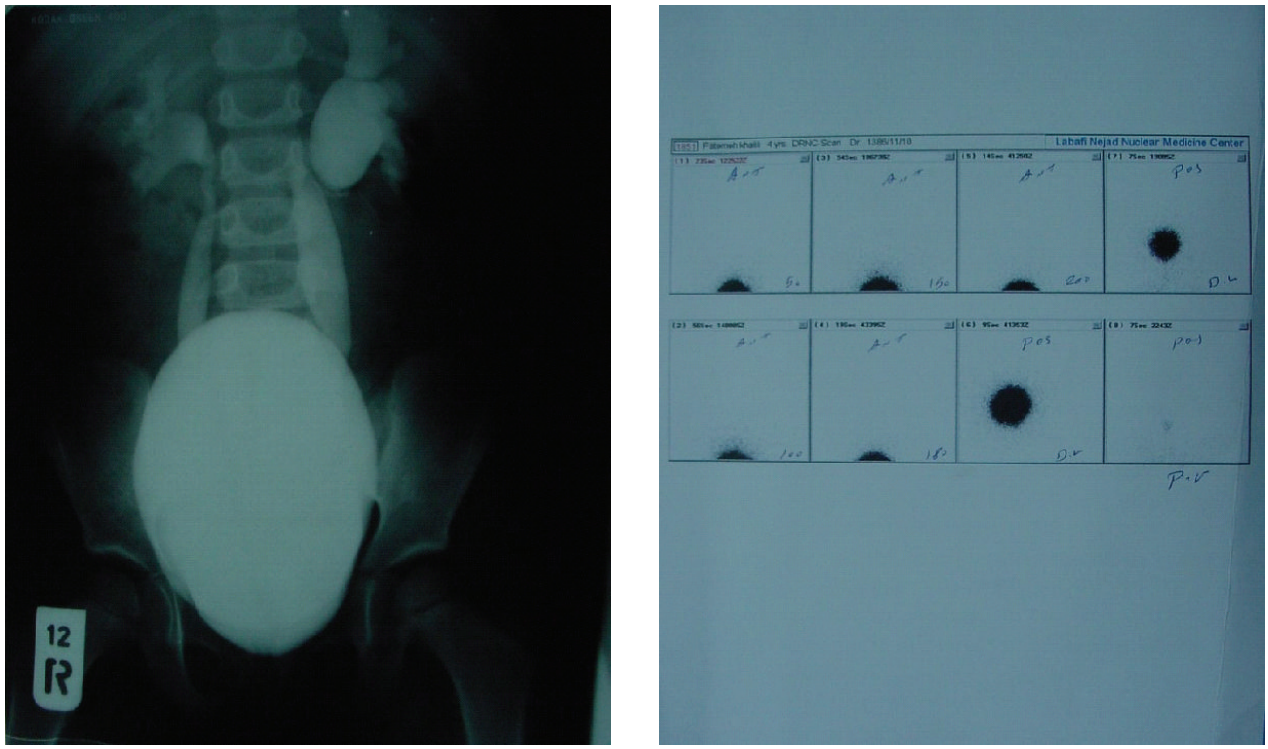
2. GIL-VERNET ANTIREFLUX TECHNIQUE

Gil-Vernet introduced his technique for antireflux surgery in 1984. He reported his experience in 38 patients with 94% success rate [35]. This technique is based on the sphincteric action of intrinsic muscular fibers of the transmural ureter, and additional muscular backing and intramural length provided by medial advancement of the ureters. Bladder mucosa is incised between ureteral orifices in a transverse fashion, and detrusor is taken down. Medial aspects of ureters are freed carefully from their surrounding tissues to be prepared and mobilized for advancement mattress sutures. Two 4-0 or 5-0 vycril mattress sutures, incorporating ureteral musculature, are placed on the medial aspect of the ureters. Mattress sutures bring ureters to the midline. It is highly influential to include ureteral musculature in the mattress sutures for prevention from late lateralization of ureters, technique failure, and VUR recurrence. Mucosa is closed vertically with interrupted chromic sutures, and the absorbable stitch is buried [35, 36] (Figure 2).

Ravasse et al. [37] reported their experience with Gil-Vernet technique in 30 children with primary vesicoureteral reflux in 1989. Patients were followed for 6–30 months. Reflux was corrected in all cases. Later several reports were published on the effectiveness of Gil-Vernet trigonoplasty. de Gennaro et al. [38] published their report on 51 children with 69 refluxing units. Mean patient age was 74 months (range from 4 months to 13 years). Reflux was grade II, III, and IV in 25, 39, and 25 refluxing units, respectively. Follow-up was performed for one year postoperatively. Surgery was successful in 97.7% of the patients. Reflux persisted in only one patient one year after the operation, in whom bilateral grade IV reflux was converted to unilateral grade III. In the study, patients were divided into 2 age groups: less than and greater than 3 years old. Success rate of surgery was 92.3% in children less than 3 years old and 100% in elder children. This finding is clearly in contrast to the assumption that Gil-Vernet technique is not appropriate for older children because of tenacious attachments of ureter in older ages [36].

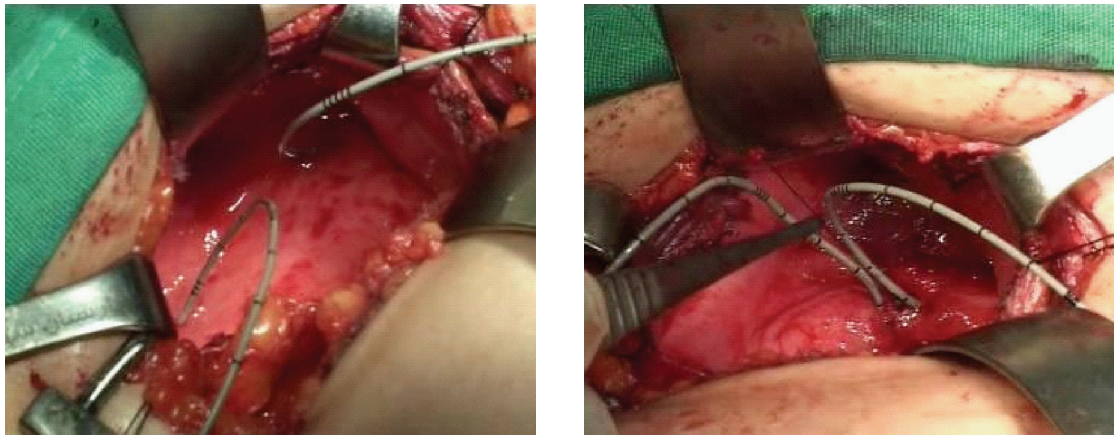
Aghdas and Akhavizadegan [32] reported on applying Gil-Vernet technique in adult women with primary vesicoureteral reflux. A total of 39 women (mean age 29 years; range 18–65 years) with 49 refluxing units were included in the study. The Gil-vernet technique was successful in eliminating reflux in 48/49 renal units (97.95% success rate) and 38/39 patients (97.43% success rate). They concluded that Gil-Vernet antireflux surgery is highly successful in adult patients.

Zhao et al. [39] described Gil-Vernet's trigonoplasty in treating vesicoureteral reflux (VUR) in neurogenic bladders. They introduced a modification in technique as advancement of transmural ureters over the midline and crossing each other in the trigone. 43 refluxing units in 26 patients with neurogenic bladder underwent modified Gil-Vernet trigonoplasty. Refluxing units had grade I, II, III, IV, and V in 5, 7, 5, 18, and 8 patients, respectively. Reflux was unilateral in 9 patients, and bilateral in 17. Success rate of surgery was 95.3%, with a follow-up period of more than 2 years in most patients. The group concluded that modified Gil-Vernet's trigonoplasty might be a useful technique in the management of patients with VUR secondary to neurogenic bladder dysfunction.



(a) (b)

Figure 1: (a) Preoperative voiding cystoureterogram of a patient with bilateral high-grade vesicoureteral reflux. (b) Postoperative RNC of the patient reveals reflux resolution.



(a) (b)

Figure 2: (a) Ureteral orifices of a patient with high-grade bilateral VUR located laterally (wide apart). (b) After performing Gil-Vernet trigonoplasty, ureteral orifices are located in the midline leading to effective detrusor support.

The presence of a duplex ureter is one of the situations which complicate reflux [40]. Various antireflux techniques have been applied to correct reflux in duplex ureters.Kazemi-Rashed and Simforoosh [33] used Gil-Vernet technique to correct reflux in 12 patients with unilateral duplicated collecting system and 18 lower pole refluxing units. Reflux was bilateral in 50% of patients. Patient mean age was 5.6 years. Reflux was corrected or improved in 94% of units.

Garat et al. [41] reported an exclusive application of Gil-Vernet technique in exstrophy- epispadias patients. Reflux is associated with bladder exstrophy due to abnormal anatomic development of the distal ureter and to a pathologic bladder disposition. Mitchell's technique allows performing bladder closure, reconstruction of epispadias and the bladder neck in one single stage. However, pyelonephritis secondary to vesicouretral reflux is the most common postoperative

complication. They applied Gil-Vernet as a first step of a bladder exstrophy repair followed by the Mitchell's technique. They concluded that combination of Gil-Vernet technique with the primary bladder closure could prevent the need for later surgical correction.

Several reports have been published on undertaking various antireflux techniques via a laparoscopic approach. Atala et al. [42] first described laparoscopic antireflux surgery using Lich-Gregoir technique in 4 mini pigs. Later, Ehrlich and Jantschek published the first reports on laparoscopic Lich-Gregoir surgery in human setting [43, 44]. Reports on laparoscopic cross-trigonal Cohen procedure have been published by Gill and Yeung [45, 46]. Okamura et al. reported their experience with endoscopic trigonoplasty but they could not achieve good results, because they did not exactly duplicate the principles used in open Gil-Vernet trigonoplasty [47]. Recently, we reported successful results following extraperitoneal laparoscopic trigonoplasty by complete duplication of Gil-Vernet open technique, achieving 93% success rate in all grades of reflux (II–IV) [34]. Regarding the simplicity of Gil-Vernet technique, it seems to be the most appropriate technique to be duplicated laparoscopically.

3. ADVANTAGES

3.1. Contralateral De novo reflux

Despite the high success rate of antireflux procedures to eliminate reflux in the operated ureter, secondary contralateral reflux is a relatively common complication occurring in 10–32% of cases [48]. Although de novo contralateral reflux resolves with time in most cases, 1.9–20% of children operated on for unilateral VUR have contralateral reflux after one year [49]. In one series, 13% of cases with contralateral reflux underwent surgical correction eventually [50]. Considerable attempts have been made to describe the possible mechanisms of developing contralateral reflux, but none of the proposed mechanisms are proven [48]. The risk for contralateral reflux is higher in patients with high grades of reflux, previous history of bilateral reflux, and duplex system [51, 52]. Some authors have recommended bilateral reimplantation for patients with the risk factors, but others have considered this as overtreatment [53]. One of the most important advantages of Gil-Vernet trigonoplasty is its bilateral nature. That is why in children with unilateral reflux; in contrast to other techniques, either open or endoscopic, Gil-Vernet trigonoplasty is the only technique that contralateral new reflux was not reported [54]. Furthermore, combination of Gil-Vernet with unilateral antireflux procedures has been recommended in several studies. Liard et al. [48] recommended contralateral meatal advancement based on the Gil-Vernet technique in patients undergoing Cohen antireflux procedure. Caione et al. [53] reported another series of patients, in whom contralateral meatal advancement was undertaken in combination with Cohen, Politano-Leadbetter, and Glenn-Anderson. Consequently, contralateral reflux was seen in none of the patients.

3.2. Ureteroscopy

A main advantage of Gil-Vernet procedure is that later catheterization of and retrograde access to the ureter can be performed normally [53]. In Cohen procedure, a highly popular and successful antireflux technique, the ureteral orifice is relocated. Alteration of the normal course of the ureter makes retrograde access to the ureter difficult [55]. Regarding almost all ureteral stones are currently treated endoscopically, the importance of easy endoscopic access cannot be overemphasized.

3.3. Catheter-free

Need for indwelling Foley catheter has been considered as a disadvantage of intravesical antireflux operations [13]. Since in extravesical Lich-Gregoir technique a catheter does not need to be left in bladder, it is associated with reduced bladder spasm and discomfort, and hematuria [13]. However, urinary retention occurs in 8%–35.6% of children after extravesical reimplantation [56, 57]. Recently, a study has described Gil-Vernet trigonoplasty without inserting a bladder catheter in 65 children with 103 refluxing units. VUR was corrected in 94.1% of patients, with no considerable complications. The authors concluded that Gil-Vernet surgery could be performed on an outpatient setting [58].

3.4. Obstruction

The most serious complication of antireflux procedure, which may require a reoperation, is ureterovesical junction obstruction (UVJO) [22]. Totally UVJO is seen in 2.5% of children underwent antireflux surgery, 2–4% after Lich-Gregoir technique, and 1% after Politano-Leadbetter [22, 59, 60]. In a report by Kliment et al. [61] on 60 children underwent Gil-Vernet surgery, UVJO was seen in none of the cases. To our knowledge, there is no report of UVJO following Gil-Vernet procedure. It is because the technique preserves the integrity of ureterovesical junction.

4. CONCLUSION

Among open surgical techniques commonly used, Gil-vernet trigonoplasty seems to be one of the least invasive. It is simple, safe, highly successful, with the advantage of possible ureteroscopy in the era of Endourology. Contralateral reflux will not follow this technique in managing unilateral reflux which is a unique advantage of this technique. The procedure could be applied in various particular situations such as neurogenic bladder, adult patients, duplex ureter, and exstrophy-epispadias. Simplicity of the technique allows undertaking the surgery laparoscopically. Several exclusive advantages of Gil-Vernet trigonoplasty make it necessary to reconsider the technique role in VUR management.

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Methodology Report

Technique of Intravesical Laparoscopy for Ureteric Reimplantation to Treat VUR

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The prevalence of vesicoureteral reflux (VUR) has been estimated as 0.4 to 1.8% among the pediatric population. In children with urinary tract infection, the prevalence is typically from 30–50% with higher incidence occurring in infancy. When correction of VUR is determined to be necessary, traditionally open ureteral reimplantation by a variety of techniques has been the mainstay of treatment. This approach is justified because surgical correction affords a very high success rate of 99% in experienced hands and a low complication rate. In that context the purpose of presenting our *surgical technique: laparoscopic intravesical ureteric reimplantation* is to highlight the use of laparoscopy to perform ureteric reimplantation for the management of pediatric VUR.

1. SURGICAL TECHNIQUE: LAPAROSCOPIC INTRAVESICAL URETERIC REIMPLANTATION

The patient is positioned supine with the legs separated apart for cystoscopy and bladder catheterization intraoperatively. For small infants, the surgeon can stand and operate over the patient's head whereas for older children, the surgeon usually stands on the patient's left side. The video column is placed between the patient's legs at the end of the table. The port placement is preceded by transurethral cystoscopy to allow placement of the first camera port under cystoscopic guidance. The bladder is first distended with saline and a 2-0 monofilament traction suture is passed percutaneously at the bladder dome under cystoscopic vision, through both the abdominal and bladder walls. This helps to keep the bladder wall from falling away when the first camera port site incision is made and during insertion of the cannula. A 5-mm Step port (Tyco Healthcare Group LP, Conn, USA) is then inserted under cystoscopic vision. A urethral catheter is then inserted to drain the bladder and start carbon dioxide insufflation to 10–12 mm Hg pressure. The urethral catheter is used to occlude the internal urethral meatus to secure CO_2 pneumovesicum, and it could also serve as an additional suction irrigation device during subsequent dissection and ureteric reimplantation. A 5-mm 30-degree scope is used to provide intravesical vision. Two more 3–5 mm working ports are then inserted along the interspinous skin crease on either side of the lower lateral wall of the distended bladder under vesicoscopic guidance (see Figure 1). A 3-4 cm long segment of an Fr 4 or 6 catheter is then inserted into the respective ureter as a stent to facilitate subsequent ureteral mobilization and dissection, and secured with a 4-zero monofilament suture (see Figure 2). Intravesical mobilization of the ureter, dissection of submucosal tunnel, and a Cohen's type of ureteral reimplantation is then performed under endoscopic guidance, in a similar manner to the open procedure.

The ureter is mobilized by first circumscribing it around the ureteral orifice using hook electrocautery (see Figure 3). With traction on the ureteric stent using a blunt grasper, the fibrovascular tissue surrounding the lower ureter can be seen and divided using fine 3-mm endoscopic scissors and diathermy hook, while preserving the main ureteric blood supply (see Figure 4). Mobilization of the ureter is continued for 2.5 to 3 cm to the extravesical space. Once

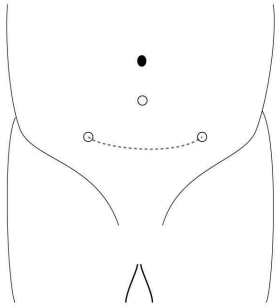

Figure 1: 5-mm working ports inserted along the interspinous skin crease on either side of the lower lateral wall of the distended bladder under vesicoscopic guidance.

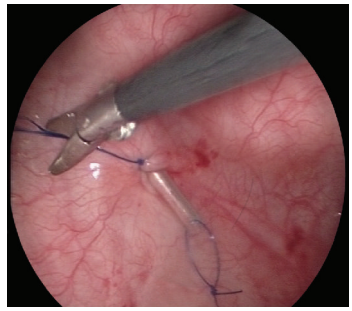

Figure 2: A 3-4 cm long segment of an Fr 4 or 5 catheter is inserted into the ureter as a stent to facilitate subsequent ureteral mobilization and dissection, and secured with a 4-zero monofilament suture.

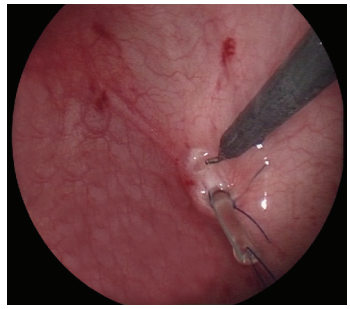

Figure 3: The ureter is mobilized by first circumscribing it around the ureteral orifice using hook electrocautery.

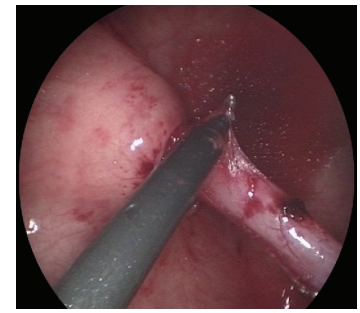

Figure 4: With traction on the ureteric stent using a blunt grasper, the fibrovascular tissue surrounding the lower ureter can be seen and divided using fine 3-mm endoscopic scissors and diathermy hook, while preserving the main ureteric blood supply.

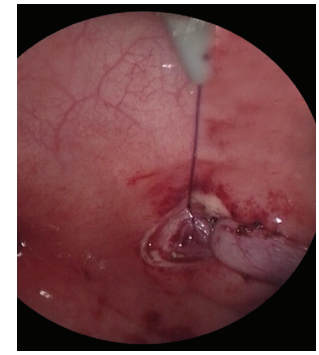

Figure 5: Once adequate ureteral length is obtained, the muscular defect in the ureteral hiatus is repaired using 5-zero absorbable sutures, usually with an extracorporeal knot-tying technique.

adequate ureteral length is obtained, the muscular defect in the ureteral hiatus is repaired using 5-zero absorbable sutures, usually with an extracorporeal knot-tying technique (see Figure 5). A submucosal tunnel is then created as in an open Cohen's procedure. Using a diathermy hook, a small incision is made over the future site of the new ureteral orifice, usually chosen to be just above the contralateral ureteral orifice. Dissection of the submucosal tunnel is then started from the medial aspect of the ipsilateral ureteral hiatus towards the new ureteral orifice, using a combination of endoscopic scissor dissection and diathermy hook for haemostasis. Once the submucosal tunnel dissection is completed, a fine grasper is passed and the mobilized ureter is gently drawn through the tunnel. Ureteroneocystostomy is performed under endoscopic guidance with intracorporeal suturing using interrupted 5-0 or 6-0 poliglecaprone or polydioxanone sutures (see Figures 6, 7). A ureteral stent is not routinely used except for selected patients undergoing bilateral ureteral reimplantation or those with megaureters requiring tapering ureteroplasty. The working ports are removed under endoscopic vision with evacuation of the pneumovesicum. The bladder-holding stitches are then tied. Each port site entry wound is then closed with a subcuticular monocryl suture.

2. RESULTS

The operative success for laparoscopic Cohen's is encouraging [1–3] and endoscopic intravesical ureteric mobilization and cross-trigonal ureteral reimplantation can be safely performed with routine pediatric laparoscopic surgical techniques and instruments under carbon dioxide insufflation of the bladder [1].

We have not faced any major complications with this technique. In the early part of the series when the cannulas were not secured to the bladder wall, displacement of the

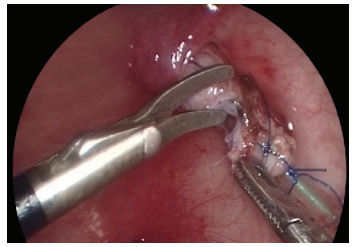

Figure 6: Ureteroneocystostomy is performed under endoscopic guidance with intracorporeal suturing using interrupted 5-0 or 6-0 poliglecaprone or polydioxanone sutures.

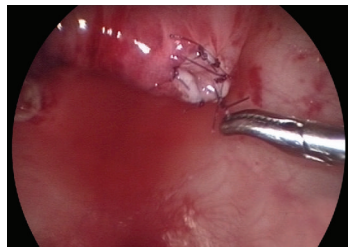

Figure 7: Completed ureteroneoctostomy.

port outside the bladder wall occurred. This resulted in gas leakage into the extravesical space, with compromise of the intravesical space and endoscopic vision. It is usually possible to reintroduce the ports but securing the ports perfectly is the key to the success of this technique [1]. We have experienced mild to moderate scrotal and suprapubic emphysema immediately postoperatively, which subsided spontaneously within 24 hours. Persistent mild haematuria up to 72 hours has also been observed, which too settles spontaneously. A recent series has reported complications of postoperative urinary leak in (12.5%) and ureteral stricture at the neoureterovesical anastomosis in (6.3%). This series also reported higher complications in patients 2 years or younger with bladder capacity less than 130 cc. [2].

3. DISCUSSION

Laparoscopic surgery has gradually made its place in surgically dealing vesicoureteral reflux. Laparoscopic extravesical and intravesical surgeries have shown good early results [1–3]. It also showed that children benefit from the improved cosmesis, more rapid recovery, and decreased postoperative analgesia requirements with the laparoscopic technique. Initial experience reported increased operative time and a steep learning curve [2], but these issues have been overcome with greater experience [1]. Greatest technical merit with high level of surgical precision is required to do this surgery. The operation desires extreme care, gentleness, and tissue respect while dissecting out the ureters. Great care needs to be taken to prevent damage to the ureteric vascularity which is an important cause which leads to developing ureteric necrosis and strictures. Laparoscopy aids fine dissection of the ureter and the submucosal tunnel with minimal trauma to the bladder wall and mucosa. The bladder can be quickly rehabilitated after surgery and normal voiding is ensured in the long term. To obtain the highest possible success with this operation, the decisive technical details described should be meticulously observed [1] supported by very good laparoscopic reconstruction skills to achieve these results.

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Methodology Report

Laparoscopic Extravesical Ureteral Reimplantation: Technique

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Recommended by Hiep Nguyen

Laparoscopic extravesical ureteral reimplantation in children is currently a technically demanding procedure with sparse literature to aid in mastering the learning curve. We present our most recent technique and lessons learned after 20 cases in children 4–15 years of age. The literature is also reviewed to encapsulate the current state-of-the-art.

1. INTRODUCTION

Open extravesical ureteral reimplantation is a successful and well-tolerated procedure with a proven track record in the surgical management of vesicoureteric reflux (VUR). Nevertheless, the relentless pursuit of minimally invasive ideals has led to the development of alternatives. Most recently, the endoscopic injection techniques have become quite popular, but concerns remain over the success rate and long-term efficacy. Thus, the laparoscopic approach offers another option which improves on the open procedure with better cosmesis and convalescence, while providing a durable and successful procedure compared to injection therapy.

Despite multiple reports in the early 1990s of experimental surgery in animal models [1–3] and few cases in humans [4, 5], it was not until the seminal contributions of the late Leo Fung in 2000 that the technical aspects and outcomes of the procedure were documented [6]. Since then, the peer reviewed literature has been sparse, such that the learning curve of this procedure is not well established. We review our current experience and lessons learned in the process.

2. MATERIALS AND METHODS

2.1. Patients

A total of 20 children aged 4–15 years (mean 7.3 years) have undergone laparoscopic extravesical ureteral reimplantation over a 5-year period. The subjects were mostly female (15 of 20) with 11 (55%) cases being bilateral. All cases were diagnosed with VUR after urinary infection and the indication for surgery included breakthrough infection in 18 of 20 and persistent high-grade VUR in 2 of 20.

The highest grade of reflux per patient ranged from 2 to 4, with only 1 case of unilateral grade 2, that being a case of failed injection therapy. The distribution of VUR per patient by highest grade was grade 4 in 7 patients (35%), grade 3 in 10 (50%), and grade 2 in 3 (15%). Megaureters, duplicated ureters, and neurogenic bladders were excluded initially. Previous open ureteral surgery remains an exclusion criterion. Bilateral cases are selected such that one side is not high-grade VUR, so as to minimize the risk of urinary retention. This hypothesis is based on the postulates that bladder dysfunction should not occur with unilateral extravesical dissection, and that high-grade VUR is a risk factor for postoperative bladder dysfunction [7].

The postoperative follow-up regimen includes a routine abdomino-pelvic ultrasound 1 month after surgery and a voiding cystourethrogram 3 months after surgery, with maintenance of antibiotic prophylaxis until the VCUG is done. In the absence of new findings on the first post-op ultrasound, another routine abdomino-pelvic ultrasound is planned 1 year after surgery.

2.2. Technique

We find it useful for learning purposes to divide the case into four specific tasks: 1-access, 2-uretero-vesical junction exposure, 3-detrusor tunnel dissection, and 4-tunnel suturing.

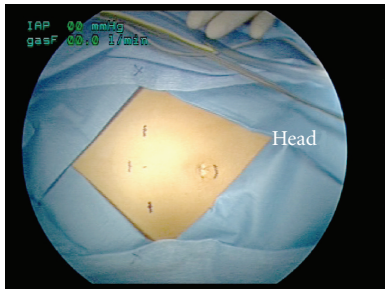

Figure 1: Port placement.

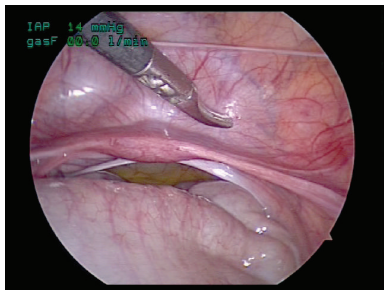

Figure 2: The peritoneal envelope is opened just adjacent to the bladder.

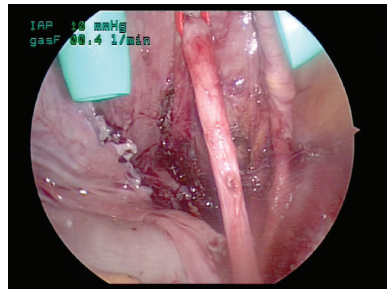

Figure 3: The ureter is mobilized while the assistant maintains traction with a vessel loop.

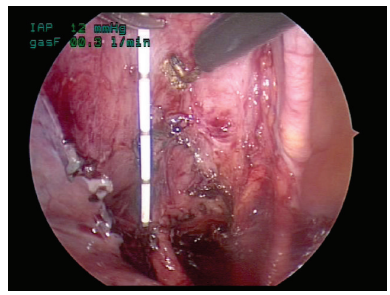

Figure 4: The tunnel should be oriented vertically and its length can be measured with a piece of ureteral catheter acting as a ruler.

2.3. Access

A 4-port approach is utilized with the patient in Trendelenburg position, legs spread apart, and the arms tucked in at the side. A sterile Foley catheter is placed in the operative field and controlled with a Toomey syringe. A mechanical bowel preparation can be helpful in patients with constipation. The first port is supraumbilical, and the 3 others form an arc along the level of the anterior-superior iliac spine (Figure 1). The level of this arc is adjusted downwards as the patient age increases and the bladder is further from the umbilicus. The arc is formed by 1 port on either lateral edge of the rectus and 1 midline port. All ports are 5 mm except for the 3 mm inferior midline port. A zero degree telescope is placed at the upper edge of the umbilicus with 2 video monitors at the foot of the bed. The surgeon and assistant are contralateral to the ureter with the assistant holding the camera while seated caudal to the surgeon.

2.4. Exposure of the ureter

The peritoneal envelope is opened just adjacent to the bladder, caudal to the Fallopian tube or vas deferens in the male (Figure 2). The round ligament is also divided to further open the peritoneal window. The ureter is readily identified by *blunt* dissection adjacent to the bladder, often with the superior vesical artery coursing parallel. The assistant then controls the ureter with a vessel loop (Figure 3) through the inferior midline port which provides the exposure needed for the surgeon to mobilize the ureter from the pelvic brim to the uretero-vesical junction.

2.5. Detrusor tunnel dissection

The bladder is partially filled via the Toomey syringe, and the planned detrusor tunnel is exposed with 2 percutaneously passed suspension sutures of 3–0 silk. A fascial closure device is utilized to pass the hitch stitch percutaneously after an appropriate exit site has been chosen. These hitch stitches are placed on either side of the apex of the planned tunnel and should be angled so as to provide a distraction force to the edges of the detrusor tunnel. The direction of the planned tunnel should be oriented vertically and its length can be measured with a piece of ureteral catheter acting as a ruler (Figure 4). The direction of the tunnel is crucial in determining subsequent ergonomics of both tunnel dissection and suturing.

The planned tunnel is scored with cautery and the superficial detrusor then cauterized. The remaining detrusor fibers are sharply divided with scissors from apex of the tunnel towards the ureterovesical junction (Figure 5). Careful hemostasis is needed to maintain exposure. The dissection on the right side is easier for a right-handed surgeon. The left side tunnel dissection is done with the scissor in the left lateral port and controlled with the left hand. The right angle forcep and right angle electrocautery can also be very helpful during the dissection around the ureterovesical junction. The amount of mucosal bulging can be adjusted by the volume of bladder filling or via the intraperitoneal insufflation pressure. Any holes in the mucosa can be closed with a figure of eight stitch of 5–0 plain. The mucosal edges of the detrusor tunnel are not undermined.

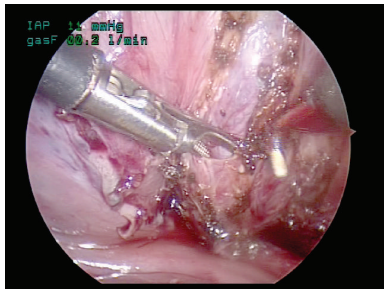

Figure 5: Dissection of the submucosal tunnel.

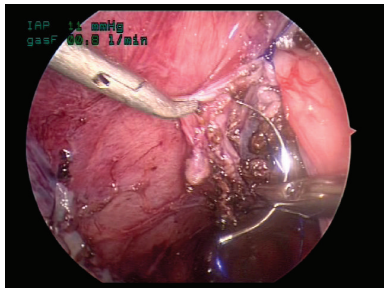

Figure 6: Suturing is back-hand with the instruments medial to the ureter.

2.6. *Tunnel suturing*

The ureter is then advanced into the detrusor trough, and the first stitch defines the neohiatus. That stitch is then held by the assistant, while the remainder of the detrusor tunnel is closed. The bladder is emptied, and the detrusor tunnel closed with interrupted 5–0 PDS suture on a RB1 needle. The suture is controlled with a 3 mm angled forcep and 3 mm needle driver. All suturing is back-hand with the instruments medial to the ureter (Figure 6). Interrupted stitches alternate from each end of the tunnel with the last stitch placed in the mid-tunnel so as to avoid inadvertent suture of the underlying ureter. Having completed the reimplantation, the bladder traction sutures are released, and the bladder is cycled to confirm the absence of a urine leak or kinking of the ureter at the neohiatus. A closed suction drain is left in cases, where the mucosa was opened. The bladder catheter is removed the following morning.

3. RESULTS

All patients who have been studied postoperatively with a voiding cystourethrogram (VCUG) have had resolution of reflux, with 2 cases refusing the post-op VCUG and 1 being lost to follow-up. One case developed de novo contralateral grade 2 VUR. Three cases were converted to open surgery, the first 2 cases, both bilateral, because surgical time had surpassed 4 hours. Case 7 had a nonneurogenic neurogenic bladder with a severely hypertrophied detrusor which made tunnel dissection difficult.

The first 5 cases, 4 of which were bilateral, can be considered the learning curve with operative times falling consistently below 3 hours for a unilateral case, and 5 hours for a bilateral case thereafter. Mucosal perforation remains the main determinant of operative time, in its absence the operative time averages 2 hours per ureter. Mucosal perforation also remains the main determinant of hospital stay. The usual case is discharged the following day after having voided, whereas those with suction drains remain for an extra day of observation. Three cases have had a mucosal perforation including cases 4, 6, and 20, none of which leaked postoperatively. There has been 1 complication, that of a distal ureteral necrosis in case 5 which necessitated open revision with a Boari flap. In this case, the ureter was held on prolonged traction with a Babcock clamp, which is no longer used. None of the cases have experienced postoperative voiding dysfunction.

4. DISCUSSION

A few technical aspects merit greater commentary, especially where there may be differences with other authors. To begin, though exposure of the ureter is fastest from the bladder up to the pelvic brim, it may be helpful for the first few cases to mobilize the ureter from the pelvic brim caudally until one is familiar with the anatomical orientation of the juxtavesical ureter. Cystoscopically placed ureteral catheters are not necessary though they were used in the first few cases to document that the ureter was not obstructed by an errant detrusor suture. The direction of the detrusorotomy should be straight up; a medial orientation will lead to kinking of the ureter whereas a lateral orientation makes for tedious dissection of the submucosal tunnel. The inverted Y-type detrusorotomy is used sparingly so as to limit the chances of mucosal injury. Instead, the detrusor tunnel edges are reapproximated with sutures further away from the ureterovesical junction, so as to limit ureteral obstruction by compression. If there is tension with the closure, a limited inverted Y-type dissection is performed.

Though all other authors describe the use of a single traction suture, this author believes that the use of 2 suspension stitches provides superior exposure of the mucosa as dissection progresses. In addition, the method of traction suture placement deserves greater attention. Most authors describe percutaneous passage of a Keith needle into the abdomen, whereas this author passes an intracorporeal suture extracorporeally with the use of a fascial closure device. This approach permits one to better judge the exit site of the stitch based on optimal exposure and orientation. The opposite and more commonly described approach commits the surgeon to an exit site before one has a chance to test the effect on bladder exposure. The direction of tunnel dissection is ergonomically best from the neohiatus downwards towards the ureterovesical junction. Unfortunately, this can lead to nuisance bleeding obscuring the exposure of the remaining mucosa. Ideally, one would want to dissect from the ureterovesical junction upwards towards the neohiatus that way the bleeding does not obscure vision, which is impossible with rigid instruments. Perhaps this is an area where the superior dexterity of the robot may be of benefit.

Considering the multiple options for the surgical management of VUR currently available, the indications for a laparoscopic extravesical approach are debated. The families electing to choose this option are concerned with the success rate of injectables and the mounting evidence that the product is not durable over the long term. These families want a successful procedure so as to avoid multiple postoperative VCUG's or to minimize the risk of another pyelonephritis in those who have experienced recurrent pyelonephritis. The advantages of reduced pain and convalescence are less in the infant population such that the procedure is offered mainly to school age children. Cosmetic considerations become more important in the postpubertal population. As a result of this selection process, the case load is smaller relative to the overall cohort of surgically managed VUR, which does impact on operative time.

Having chosen a laparoscopic approach, other considerations include whether to use a transvesical approach or an extraperitoneal approach. Though the extravesical approach is ideally suited to an extraperitoneal exposure, this author feels that the extra surgical time involved in creating the space is not warranted. When one considers that the bowel is not mobilized and that the peritoneal window used for transperitoneal exposure is so small, it is difficult to imagine significant adhesions occurring in such a context. I have been impressed in the cases converted open at how small the peritoneal window was; in fact the bowel did not enter the wound. Likely for these reasons, there are no published reports on extraperitoneal ureteral reimplantation, though extraperitoneal pelvic laparoscopy has been reported for various procedures [8].

The transvesical approach with pneumobladder was first described by Okamura et al. with the technique of endoscopic trigonoplasty [9]. This procedure has been abandoned both by the original authors and others [10–13]. The idea of a pneumobladder was advanced with the initial attempts at endoscopic Cohen procedure [12, 14]. This approach has gained popularity [15–17], likely due to concerns over voiding dysfunction with bilateral extravesical surgery. The largest series to date was recently reported by Canon et al. [18] with acceptable outcomes, though the success rate was less than open surgery. It remains to be seen if the morbidity of laparoscopic unilateral transvesical surgery is greater than the laparoscopic extravesical approach, similar to the open experience. Despite a large case load and experience, Canon et al. still needed a bladder catheter for at least 36 hours, likely due to the multiple bladder perforations. In addition, with proper patient selection, the extravesical approach can be used bilaterally without voiding dysfunction. Our favorable experience with laparoscopic bilateral extravesical ureteral reimplantation is corroborated by that of Lakshmanan and Fung [6] and that of McAchran and Palmer [19] with the open extravesical approach.

Laparoscopic extravesical ureteral reimplantation was popularized by Lakshmanan and Fung [6] with excellent outcomes in their series of 47 patients and 71 ureters. They reported a 100% resolution rate of VUR, though operative times were not documented. Unfortunately, they also experienced 3 cases of distal ureteral necrosis and emphasized that the Babcock clamp should not be used for control of the ureter. Based on this author's personal experience as well, I would strongly concur. Since then, Shu et al. [20] have published excellent outcomes in a postpubertal cohort of 6 female patients. They comment on how the laparoscopic approach to the pelvis is relatively easier than open pelvic surgery in adolescents, an opinion shared by this author. The excellent outcomes with extravesical reimplantation have been further corroborated in a more challenging set of patients including duplicated ureters [21], dismembered ureteral tailoring [22], and psoas hitch as an adjunct [23].

Nevertheless, in most series, the occasional problem of mucosal perforation and its attendant prolonged catheter drainage persists in comparison to open extravesical surgery. It remains to be seen if the ergonomic advantage of robotic assistance will be helpful in this regard. Improvements in instrumentation such as a hook electrocautery which is shielded posteriorly and thus does not cause mucosal perforation by thermal injury would be of tremendous benefit. Furthermore, prospective experimental study of the facility of mucosal exposure at different insufflation pressures and different bladder filling volumes deserves greater attention.

5. CONCLUSIONS

Laparoscopic extravesical ureteral reimplantation is another option in the surgical management of vesicoureteric reflux. It offers a greater success rate and durability compared to injection therapy, while offering cosmetic and convalescence advantages over open surgery in the older child. The learning curve of the procedure is reasonable and facilitated by an analysis based on 4 components, namely, access, ureter exposure, tunnel dissection, and tunnel closure. The component of tunnel dissection is the only one which could benefit from further improvement, likely accomplished with refinements in instruments or greater study of the variables which contribute to mucosal perforation.

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Methodology Report

Vesicoscopic Ureteral Reimplantation: A Minimally Invasive Technique for the Definitive Repair of Vesicoureteral Reflux

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Recommended by Hiep Nguyen

The surgical treatment of vesicoureteral relfux can range from injection therapy to open ureteral reimplantation. Minimally invasive applications for treatment of vesicoureteral relfux include laparoscopic extravesical and intravesical ureteral reimplantation. We present our extended experience of the technique for intravesical cross-trigonal ureteral reimplantation for vesicoureteral relux.

1. INTRODUCTION

As in all areas of surgery, there is an ever increasing interest in minimally invasive techniques. Injection therapy using dextranomer/hyaluronic acid is a simple technique with low morbidity but most studies would suggest that this approach is not as successful as standard repair. Laparoscopic reconstructive surgery, for whatever underlying pathologic condition, has the expectation and advantage that as one tries to follow the same principles as with open repair, after the learning curve period, success rates should be identical.

Most reports of laparoscopic repair of reflux have described the use of an extravesical technique with relatively good success rates. Many urologists however prefer to correct reflux using an open transvesical approach. The feasibility to replicate this technique using a vesicoscopic approach was demonstrated by Gill et al. [1] Yeung however was the first to present a large series of patients undergoing cross-trigonal ureteral reimplantation using CO_2 pneumovesicum with success rates nearly identical to standard open repair [2]. Simiarly, Valla et al. reported their experience with this technique again demonstrating high success rates [3]. Kutikov et al. presented their initial experience with vesicoscopic reimplantation for both primary reflux and megaureter repair [4]. A retrospective review from our center has demonstrated decreased pain in patients undergoing a vesicoscopic approach compared to standard Cohen repair [5]. In this report, we present our extended experience with vesicoscopic cross-trigonal ureteral reimplantation.

2. MATERIALS AND METHODS

2.1. Patient selection

Our preference is to use this technique only in children with primary reflux (less than grade IV) who have seemingly normal bladder function based on clinical history or have dysfunctional elimination syndrome responsive to standard treatments. Though there are some published reports of using a vesicoscopic technique for megaureter repair, we have elected to use this technique only in situations where tapering would not be needed. We have performed this procedure in children as young as 13 months, but there realistically may not be much of an advantage in performing vesicoscopic repair in children less than 2 years of age. The decreased working space in younger children does make the procedure more technically demanding and may obviate the advantages of vesicoscopic repair. Preoperative bladder volume was not utilized to evaluate inclusion criteria for surgical consideration. Failed injection therapy does make dissection more complicated but should not be considered a contraindication.

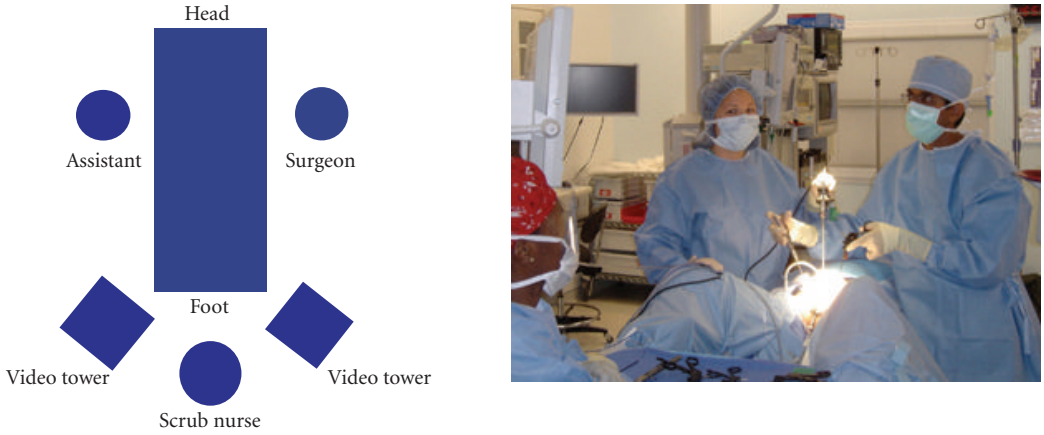


Figure 1: Patient is placed in dorsal lithotomy position with the surgeon standing to the patient's left looking at a monitor over the right leg.

2.2. Surgical technique

Positioning

The procedure is performed with the child in the dorsal lithotomy position with the abdomen and perineum within the sterile field (Figure 1). Urethral access is needed at various times during the procedure. Due to the extended length of the procedure, careful positioning and padding of the legs is needed to prevent nerve palsy.

The surgeon typically stands on the patient's left side with the monitor positioned over the right leg. The assistant, that is, camera holder, stands on the patient's right looking at a monitor positioned over the left leg. The scrub nurse typically stands between the legs.

Bladder wall fixation and port placement

After positioning the patient, using a pediatric cystocope rigid cystourethroscopy is performed using a 30-degree lens during the fixation of the bladder wall. Fixation of the bladder to the anterior abdominal wall is critical for several reasons. Firstly, it can be difficult to push a port through fascia and bladder wall. Fixation of the bladder will create enough resistance to allow ports to be more easily introduced. Secondly, in case of inadvertent removal of the port during the procedure, having the bladder fixed to the abdominal wall will maintain the relationship between the skin incision and the entry site within the bladder permitting replacement of the port. Pneumovesicum is created using CO_2 introduced through the irrigation port of the cystoscope at maximal pressures of 10–15 mm Hg. Once the bladder is maximally distended, under cystoscopic guidance the dome and lateral walls of the bladder are fixed to the abdominal wall. The present technique for placement of the fixation sutures is adapted from a report on percutaneous internal ring suturing, a method for percutaneously closing the patent processus vaginalis in children with inguinal hernias or communicating hydroceles [6]. Briefly, a 2-0 PDS suture is placed through an 18 guage spinal needle. Under cystoscopic guidance, the spinal needle is introduced into the bladder (Figure 2(a)). This will naturally push the suture into the bladder. Upon extraction of the needle, a loop of suture, called the pulling loop, will be left in the bladder. Through an adjacent puncture, the spinal needle is inserted into the bladder and through the pulling loop (Figure 2(b)). One end of the suture that formed the pulling loop is then inserted through the needle, thus placing it through the loop (Figure 2(c)). Retracting the pulling loop out of the bladder pulls the free end of the suture creating a through-and-through suture which can be tied fixing the bladder to the abdominal wall (Figure 2(d)). Fixation sutures are placed in the midline as well as the lateral walls of the bladder. A 5 mm port is placed in the midline for the camera and two 3 mm ports placed laterally for the working ports. These ports are placed immediately distal to the fixation sutures in the direction of the bladder neck. It is often helpful to place a purse string suture around the ports to further immobilize them, minimizing the chances for inadvertent removal. For most children, 3 mm laparoscopic instruments that are 20 cm in length are ideal.

Ureteral dissection

Vesicoscopy is performed using a 5 mm 30-degree lens. The orientation is such that the bladder neck will be located at the 12:00 position (Figure 3). Feeding tubes (3.5 Fr.) are placed per urethra, passed up each ureter, and fixed with fine suture. Dissection is begun by using a hook electrode at a power setting of 10 (low power) (Figure 4(a)). Lifting up on the suture holding the feeding tube in place will create sufficient tension such that incision of the bladder mucosa with the hook electrode will cause the bladder to fall back. In a manner analogous to open transvesical surgery, the ureter can be mobilized from the surrounding detrusor muscle using a combination of sharp and blunt dissection. Extreme care must be used when transecting investing bands of detrusor and it may be safer to divide these bands sharply

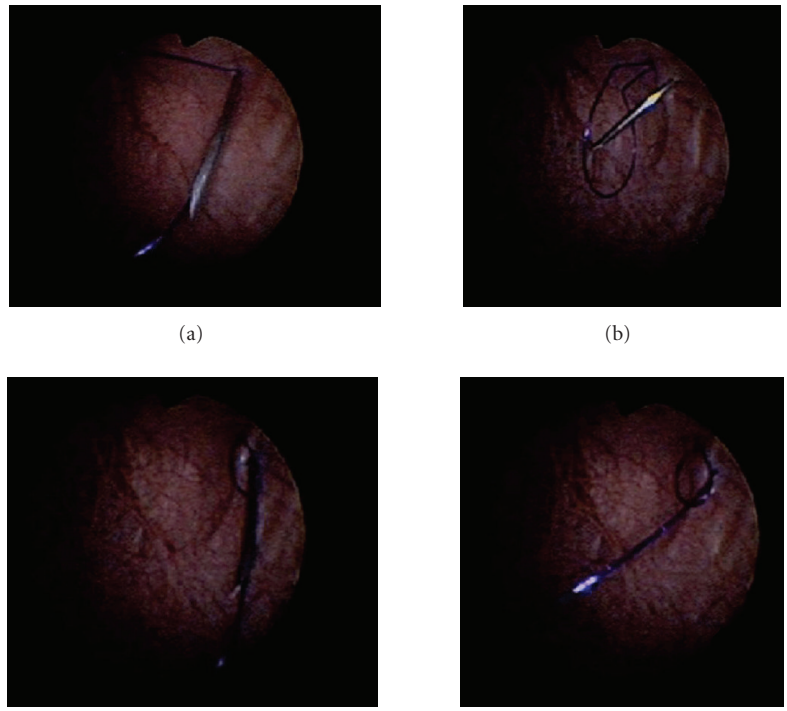


Figure 2: (a) Spinal needle has pushed suture into bladder creating pulling loop. (b) Spinal needle passed through pulling loop via an adjacent puncture. (c) With needle through pulling loop, one free end of the suture is passed through spinal needle and thus the pulling loop. (d) Removal of spinal needle results in suture being snared by pulling loop. Subsequent retraction of pulling loop creates through-and-through suture which can then be tied fixing bladder to abdominal wall.

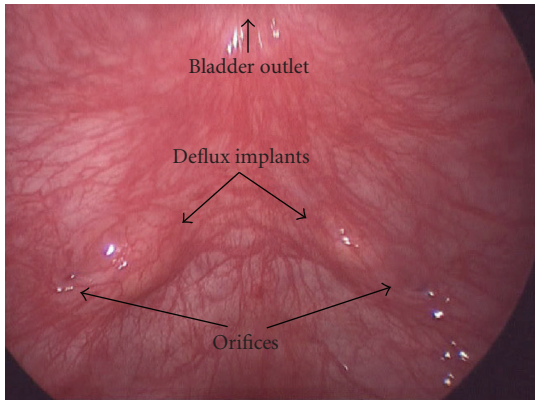


Figure 3: Initial "vesicoscopic" view of operative site in a patient that had failed prior injection therapy.

as opposed to using cautery (Figure 4(b)). This dissection is rather easy and rapid in children with thin-walled bladders but can be quite difficult if a child has a markedly thickened bladder wall. Dissection is continued until enough length is gained to bring the ureter to the contralateral side (Figure 4(c)). The posterior detrusor opening is then closed with interrupted 4-0 polydioxanone suture. For bilateral repairs, the contralateral ureter may then be mobilized (Figure 4(d)).

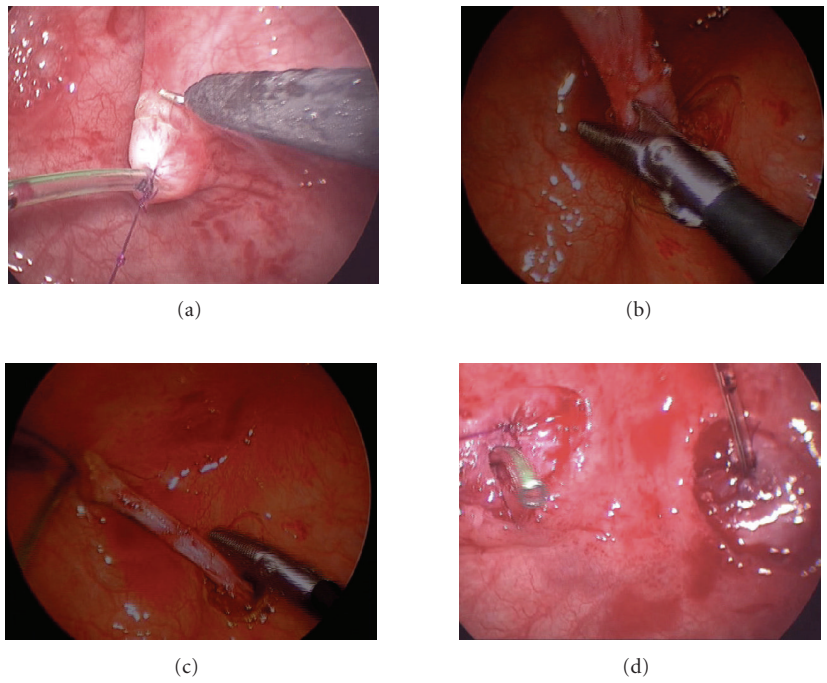
During the procedure a suction device is needed to remove not only blood but also urine that may accumulate at the bladder base. Some authors have left a small urethral catheter indwelling to assist with suction but our preference is to simply use a 3 mm suction-irrigation device through one of the working ports as needed.

Tunnel creation

Cross-trigonal tunneling is then performed with a combination of blunt and sharp dissection in the submucosal plane (Figure 5(a)). Maryland graspers are used to elevate the mucosa and fine scissors are used to initiate and develop the plane. The positive pressure within the bladder along with the optics of the 30-degree lens can assist with the visualizing the appropriate plane. The length of the tunnel created spans from the initial hiatus across to the contralateral hiatus. After creation of the tunnel(s), the ureters may be placed in the tunnels and passed to the other side. The ureter(s) is then fixed in place with 5-0 polydioxanone suture (Figure 5(b)). The remaining mucosal openings are then closed with absorbable sutures and the feeding tubes removed (Figures 5(c) and 5(d)).

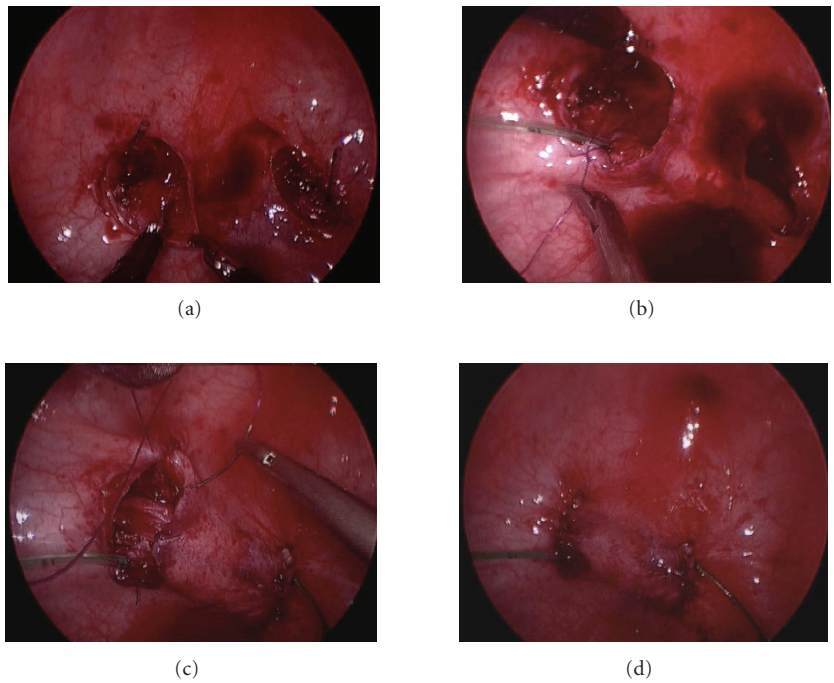
Bladder port closure

To maintain the pathway through the incision into the bladder, a feeding tube is placed through each port prior to



(a) (b) (c) (d)

Figure 4: (a) Initial dissection with hook electrode at low-power setting. (b) Investing detrusor bands divided using sharp dissection. (c) Ureter has been mobilized such that it can reach the contralateral side with no tension. (d) View after bilateral mobilization and closure of the posterior detrusor openings. Ureters have been pushed back out of bladder to permit visualization of the bladder mucosa-detrusor plane to permit creation of the submucosal tunnels.



(a) (b) (c) (d)

Figure 5: (a) Creation of the submucosal tunnels started by gently lifting up on mucosa and sharp dissection of the appropriate plane. (b) The right ureter has been passed through the tunnel and sutured to the original hiatus on the contralateral side. (c) Both ureters have been transposed and sutured in place. The left mucosal opening is then closed with absorbable suture. (d) Completed repair prior to removing feeding tubes.

its removal. Under cystoscopic guidance, the bladder ports are closed using sutures placed in a manner analogous to the initial fixation sutures. After placing the bladder port closure sutures, a foley catheter is inserted to decompress the bladder and the fixation sutures are removed. This allows the bladder to fall away from the abdominal wall. The bladder port sutures are then carefully tied and the skin incisions subsequently closed.

The foley catheter is typically removed in 36 hours. Followup imaging included renal ultrasonography at one month and cystography at 3 months.

3. RESULTS

To date, 103 children have undergone attempted vesicoscopic correction. Due to poor port placement, three were converted to open repair leaving a total of 100 patients who did undergo vesicoscopic ureteral reimplantation. There were 91 girls and 12 boys with ages ranging from 13 months to 18 years. Grade of reflux ranged from I to IV. Ten of these children had failed injection therapy with dextranomer/hyaluronic acid. Seventy-eight underwent bilateral repairs and 25 unilateral. Twelve of these patients had duplex systems and underwent common sheath reimplants.

To date, 77 patients have undergone postoperative cystograms and 72/77 (94%) had normal studies. One of these with persistent reflux developed contralateral reflux after unilateral reimplantation. The other four occurred early in the series, within the first 30 patients. Cystoscopy in three of these demonstrated either small ureterovesical fistulae or an absent intramural ureter, suggestive of ischemic injury. Subsequent modification of the ureteral dissection technique has led to no further cases of persistent reflux in the last 47 post-operative cystograms performed.

Two patients did develop postoperative ureteral obstruction requiring temporary percutaneous nephrostomy tube placement. These patients had imaging studies that suggested extrinsic compression from retrovesical urinomas. One patient underwent reoperative ureteral reimplantation at another center and one resolved with stent placement. One patient developed small bladder stones which passed spontaneously. The first patient in the series, who did not have the bladder ports closed separately, did develop a small extraperitoneal leak which healed with bladder drainage. All subsequent cases have had bladder ports closed with no further port site leaks.

Intraoperative complications included proximal ureteral migration of the feeding tubes in four patients necessitating immediate ureteroscopy for retrieval. Pneumoperitoneum occurred occasionally and was treated by intraoperative intraumbilical Veress needle placement.

4. DISCUSSION

There is an ever increasing interest in the application of minimally invasive techniques for surgical reconstruction. In many centers there is a wealth of experience in the laparoscopic management of such diverse conditions such as impalpable testes, nonfunctional kidneys, ureteropelvic junction obstruction, and duplex anomalies. However, very few centers have attempted laparoscopic correction of vesicoureteral reflux. There are many possible reasons for this. First and foremost is that standard open surgical correction works so well. It has an extremely high success rate with minimal morbidity. Furthermore, cosmesis is not an issue as typically a small transverse suprapubic incision is required.

If standard ureteral reimplantation is so effective with such minor morbidity, why consider laparoscopic, or rather a vesicoscopic approach? We feel that there may be several advantages. Firstly, we have shown in a retrospective report that patients undergoing vesicoscopic repair have decreased analgesic requirements compared to after open repair. Secondly, it has been our observation that parents are often much more accepting of having definitive surgical correction for their children if they know it will be done "laparoscopically." Thirdly, in a training center, vesicoscopic reimplantation can be very effective at developing and teaching high-level surgical techniques since careful dissection and fine suturing need to be done, and all within the confines of the bladder.

The ultimate benefit of a surgical procedure must be decided based on a review of the surgical success and rate of complication. After utilizing a very similar technique, Yeung et al. demonstrated results equivalent to open ureteral reimplantation (96% VUR resolution) in a smaller series in children. Valla et al. demonstrated success rates of 92%. Kutikov et al., detailing their early experience, had a 93% success rate. Our present overall success rate is at 94%. However, all of our failures occurred in the first half of our series. Cystoscopic evaluation of the failures demonstrated evidence of possible ischemic injury to the ureters. We subsequently modified our dissection technique and have had no further failures in the last 47 patients tested. Thus with experience gained and lessons learned, we think that vesicoscopic reimplantation is essentially equivalent to open Cohen reimplantation with regard to efficacy of correcting reflux.

Ureteral obstruction may be the most feared complication with ureteral reimplantation and, at least with open surgery, is usually due to ischemic stricture formation or inappropriate angulation through the detrusor neohiatus. In our series we did have two patients with postoperative obstruction related to retrovesical urinomas. We suspect this was due to improperly performed ureterovesical anastamoses with leakage of urine through submucosal tunnel.

Though there are some reports on the use of a vesicoscopic approach for megaureter repair, we have elected not to do this. Firstly, in our experience, it is very rare to need to taper a ureter in the first place. Secondly, a carefully performed tapered reimplantation is difficult enough and in a training institution, our preference is to ensure that our residents and fellows can do a quality open megaureter repair.

With the experience gained in this series, we have applied certain modifications to improve the procedure and its outcomes. Great care during the dissection and mobilization of the affected ureters is necessary to prevent ureteral injury. A low power setting on the hook electrode is mandatory. As

there is no fourth port for an assistant, one has to be careful when using electrocautery that the tissue being divided is well away from the ureter.

Port placement can be tricky. If placed too inferiorly, the ports will be right on the orifices. If placed too cephalad, the ports may traverse the peritoneum. Leakage of gas into the peritoneal cavity can occur and the subsequent pneumoperitoneum can lead to collapse of the bladder and poor visibility. Transumbilical Veress needle placement will vent the carbon dioxide and allow the bladder to distend appropriately.

Extraperitoneal urinary leakage diagnosed after the first procedure leads to the inclusion of bladder port closing sutures as outlined earlier. Since the application of this technique, no other port leaks were observed. Migration of the feeding tubes proximal to the ureteral orifice was a problem encountered four times in the study. Occasionally, the suture can pull through the ureteral orifice with traction during dissection or manipulation of the ureter. Fixation of the feeding tube to the ureteral orifice is mandatory to prevent migration of the tube. Occasionally, this requires stopping the dissection to resuture the feeding tube to the distal ureter.

Vesicoscopic ureteral reimplantation is an admittedly challenging procedure. There is a tremendous learning curve and one must exercise a great deal of dedication at wanting to learn the procedure. Though the complication rate that we note in our series is greater than that which may be seen in a contemporary series of open repairs, we suspect that this is an indication of the difficulty in learning the procedure. The adverse events that we have noted in our series are probably due to suboptimal execution of the technique rather than the concept of vesicoscopic reimplantation itself. Our positive experience in the last half of the series is indicative of the fact that vesicoscopic ureteral reimplantation is a highly effective, minimally invasive approach for the definitive repair of primary reflux.

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Research Article

Robotic-Assisted Laparoscopic Management of Vesicoureteral Reflux

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Robotic-assisted laparoscopy (RAL) has become a promising means for performing correction of vesicoureteral reflux disease in children through both intravesical and extravesical techniques. We describe the importance of patient selection, intraoperative patient positioning, employing certain helpful techniques for exposure, and recognizing the limitations and potential complications of robotic reimplant surgery. As more clinicians embrace robotic surgery and more urology residents are trained in robotics, we anticipate an expansion of the applications of robotics in children. We believe that it is necessary to develop robotic surgery curricula for novice roboticists and residents so that patients may experience improved surgical outcomes.

1. BACKGROUND

The minimally invasive surgical (MIS) approach to vesicoureteral reflux disease was first described by Atala et al. in minipigs in 1993 and then first described in humans by Ehrlich et al. in 1994 [1, 2]. Since then, few pediatric centers have embraced either the laparoscopic extravesical or vesicoscopic cross-trigonal approaches owing to the technical challenges of fine suturing in the small spaces. Success rates have been comparable to open surgical techniques and in 2004; Peters described his experience using the surgical robot as an adjunct to both transvesical and extravesical repairs [3]. Since then, urologists have watched robotic surgery becoming the standard of care in some adult urologic procedures such as radical prostatectomy, but application in pediatrics has been limited to a few centers where the robot has been accessible to pediatric urologists.

The surgical robot allows clinicians improved dexterity, three-dimensional visualization, and motion scaling, which helps dampen physiologic tremor. Due to these benefits, the reconstructive techniques required for ureteral reimplantation are well suited for robotic surgery. In addition, due to the enhanced learning curve with robotic surgery over pure laparoscopy, surgeons are able to utilize the same techniques and suture size as would be used in open surgery. Major advantages over pure laparoscopic and open techniques are 10X visual magnification and three-dimensional visualization, and the ergonomic considerations of the robot console where the surgeon sits during the procedure. The limitations of robotic surgery are the added cost to the host institution, the increased operative times required, and the support required from the ancillary operative staff. Interestingly, these limitations are the same experienced by the initial laparoscopists of the 90s.

The key aspects of successful robotic ureteral reimplantation surgery include appropriate patient selection, proper patient positioning, an armamentarium of helpful techniques to facilitate exposure, and an understanding of the limitations of the robot and the complications potentially encountered.

2. PATIENT SELECTION

In counseling our patients for the options of surgical correction of vesicoureteral reflux, we rely heavily on the individual patient's clinical picture. All patients are offered both endoscopic and formal surgical repairs, whether by minimally invasive or open techniques. We detail peer-reviewed cited and personal success experience for our patients and inform them of the variations in success that can be expected in the face of higher grades of reflux and voiding dysfunction. It is difficult to generalize or standardize patients, but typically,

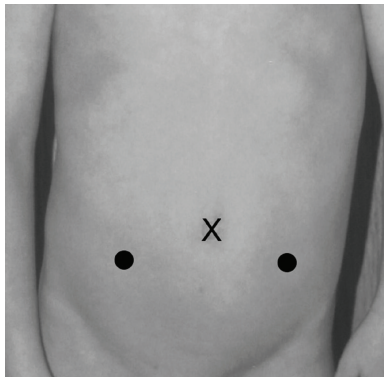

Figure 1: Port placement, bilateral reimplants. X = camera port, black dots = working ports.

formal surgical repairs are reserved for patients with higher grades of reflux, severe voiding dysfunction, or in those with duplex systems. Patients with lower grades of reflux may be more appropriate for intramural ureteral bulking agent implantation. When discussing robotic/laparoscopic techniques versus open surgical techniques, we highlight the fact that open surgery is the "gold-standard," and MIS repairs appear to have similar success rates as open surgery. Since we do not discern pure laparoscopy from robotic-assisted laparoscopy because we believe that the robot is merely another adjunct or tool to laparoscopy, we only describe that we use the robot to assist with reconstructive surgeries.

Patient comorbidities have not played a major role in the decision for robotic repairs, however, patients with severe pulmonary reserve deficits need to be carefully evaluated preoperatively by anesthesia to determine if abdominal insufflation may impair ventilation. In addition, children with prior abdominal surgery may require additional dissection in the abdomen to lyse any adhesions that may obscure the line of sight to the pelvis.

In our experience, patient's size has not limited our decision for robotic surgery in part because it is unusual to operate on children less than 6 months of age for vesicoureteral reflux and because we have not found that the intuitive working port-to-camera port distance recommendations of 8–10 cm to be applicable in small children. We have successfully used interport distances of 5 cm without any arm collisions. We believe that this is due to the small operative field and few large arm movements required once the robot is appropriately set up and docked.

3. PATIENT POSITIONING

As with all robotic surgeries in children, appropriate patient positioning is critical to the efficient progression and success of the case. Since it is our practice to perform cystourethroscopy prior to ureteral detrusorraphy surgery, we place the patient in a low lithotomy position and prep the patient for both cystoscopy and laparoscopic access at the same time. We angle the patient in 10 degree Trendelenberg to encourage the bowel to fall out of the pelvis. For bilateral repairs, we choose to place indwelling stents if the child has a history of a trabeculated thickened bladder due to voiding

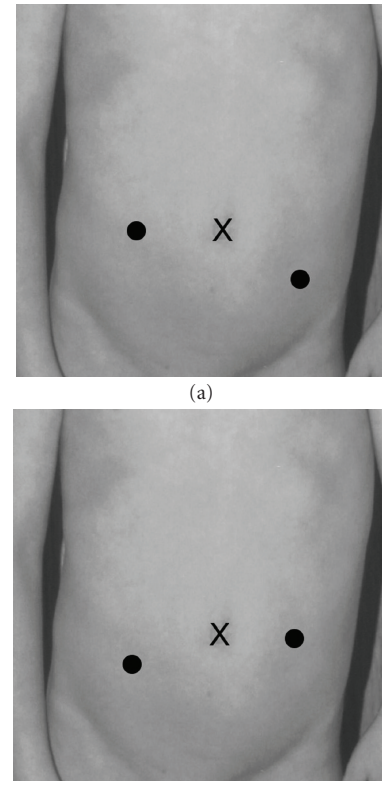

Figure 2: (a) Port placement, right reimplant; (b) port placement, left reimplant.

dysfunction as we have observed postoperative edema at the neotransmural tunnel causing transient obstruction. For the majority of cases, we typically will place external ureteral catheters attached to a urethral catheter to help guide ureteral dissection during the procedure. These are removed at the end of the surgery.

Although some institutions have used the vesicoscopic approach for ureteral reimplant surgery [4, 5], we use a transperitoneal approach because we find that working spaces are not limiting and we are more comfortable with this approach. We use a two-armed robot and place the camera port through the umbilicus. The two working ports are placed at the paramedian lines slightly below and on either side of the umbilicus to avoid the inferior epigastric vessels (Figure 1). In children less than 15 kg, we have tended to place the working ports at the level of the umbilicus to ensure a good distance to the target site. For bilateral cases, the robot is situated at the patient's feet in the midline; however, for unilateral repairs we position the robot at the ipsilateral foot. In addition, the ipsilateral working port is placed slightly higher than the contralateral working port (see Figures 2(a), 2(b)). In small infants, we place the camera port subxyphoid, to ensure a good working distance of the camera to the target site (Figure 3).

At our institution, we have found that the most efficient way to set up our robotics room is with a fixed location for the console and a relatively fixed location for the robot. We move the patient bed, the video cart, and the instrument

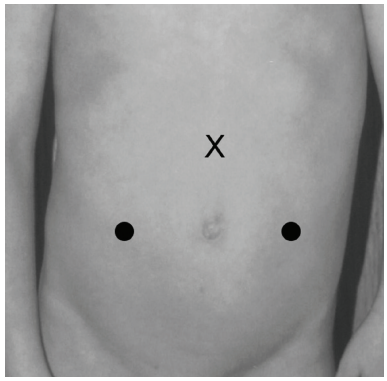

Figure 3: Port placement, small children or short-waisted children, bilateral reimplants.

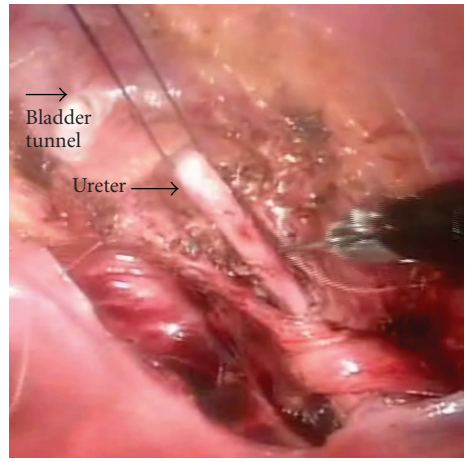

Figure 4: Demonstration of *hitch stitch* around right ureter for retraction (2-0 monofilament).

table depending on the access we desire. For reflux surgery, we position the tower on either side for bilateral repairs or on the ipsilateral side for unilateral repairs. This allows for easy access for the bedside assist and scrub tech to be on the contralateral side with the instruments. In the event that pure laparoscopy maneuvers are necessary, there is ample room.

4. INTRAOPERATIVE TRICKS

There are certain maneuvers which are unique to laparoscopic/RAL surgery which assist in expediting the surgeries and allow for the minimum number of ports to be placed. A sharp criticism of minimally invasive surgery in children, especially small children, has been that open surgery incisions are not as morbid as in adults and that the additive incisional length of minimally invasive surgeries may equal and sometimes exceed the total length of a single open surgical incision thereby theoretically causing more postoperative pain. This argument is flawed because Blinman has demonstrated that the sum tensions of port incisions do not equal the whole incisional tensile burden as conjectured by some open surgeons [6]. We believe that the smallest and fewest possible ports should be used to safely and effectively perform MIS surgery, therefore, we employ the use of hitch-stitches to assist in organ retraction throughout our cases [3]. During an extravesical ureteral reimplant, we routinely use monofilament suture placed through the lower abdominal wall to aid in retraction of ureters and the bladder (Figure 4). During creation and closure of the detrusor bladder flaps, we find that a hitch stitch to help elongate the bladder anteriorly ensures proper length and straightening of the tunnel. In addition, we use anteriorly retracted stitches around the ureters to assist in laying the ureters down in the detrusor tunnels. To lessen constant tension on the ureter with this stitch, we routinely release the tension from outside of the abdomen when retraction is not needed. When no longer needed, these sutures are removed leaving only behind small needle puncture marks on the suprapubic skin. For children with more subcutaneous fat, we lengthen the hitch stitch needles by partially flattening them (skiing).

Throughout the creation of the detrusor tunnel and the detrusorotomy, we intermittently insufflate the bladder through the indwelling urethral catheter with a second insufflation unit to ensure appropriate position of the ureter as described by Yeung et al. [7]. We have used both manual fluid bladder instillation for distention and gas insufflation and have found the gas to be more rapid in raising and dropping the bladder and in the event of a small mucosotomy which would require oversewing, the liquid distention tends to make for a more tedious closure.

5. COMPLICATIONS

With the adoption of new techniques, we have experienced some complications which can be attributed to developing familiarity with minimally invasive reimplant surgery. When counseling families about the adverse outcomes of ureteral reimplant surgery, we discuss urine leak, urinary obstruction, and urinary retention. Casale et al. have published their series of 41 bilateral extravesical RAL reimplants without any post-op urinary retention. They attribute the absence of retention, despite open surgical extravesical repair literature citing up to 10% postoperative retention, due to the improved visualization of the neurovascular bundle that is situated just lateral to the ureteral hiatus [8, 9]. On the other hand, Peters encountered postoperative voiding dysfunction in his experience of extravesical robotic reimplants [3]. We have had only one patient who had mild retention post-op and we anticipated this because of his preoperative urinary retention history so we placed a percutaneous suprapubic tube at the time of his reimplant surgery for postvoid drainage. His tube was removed 2 weeks later after his retention improved to less than 10% of his functional capacity.

Early in our experience, we had an adolescent female present one week postoperatively with unilateral labial swelling and abdominal pain. She was found to have a unilateral ureteral leak just outside of the neohiatus and required temporary stenting. The leak sealed and her reflux was successfully treated confirmed by VCUG. It is possible that electrothermy dissection near the ureteral insertion to the bladder may have caused this leak and since then, only

nonenergy dissection is used to raise detrusor flaps near the ureteral hiatus. Another child with severe elimination syndrome and a thickened bladder wall who underwent bilateral ureteral reimplants developed transient postoperative ureteral edema leading to azotemia. She required temporary ureteral stenting after which her azotemia resolved. VCUG and US after stent removal confirmed successful reflux resolution and no ureteral obstruction. In lieu of this outcome, we also advocate stenting of children with solitary kidneys to avoid the possibility of postoperative transient acute renal failure as recommended by Peters [3].

As described by Casale et al., we have encountered the uterine artery in our female patients [9]. During open extravesical reimplants, the uterine artery is rarely identified, but with abdominal insufflation, the bladder is situated anteriorly in the operative field thereby giving the appearance that the ureter must be stretched to lay down in the detrusor trough. The uterine artery will appear to kink the ureter or press it posteriorly as it is laid down in its detrusor trough. During abdominal desufflation, however, one will see that the kinking is merely an artifact of the distention.

Beyond these early complications, we have not witnessed subsequent urinary retention, urine leak, or ureteral stenosis as identified by any *de novo* hydronephrosis. In addition, we have had three VCUG-documented reflux management failures or reflux down grades and one case of *de novo* contralateral reflux out of 16 patients. All failures have been in children with varying reflux grades and the only common element of these children has been a history of preexisting elimination syndrome, a factor well known to reduce antireflux surgery success.

6. FUTURE PERSPECTIVES

Initial reports of the success of RAL reimplant surgery seem to rival open surgical repairs. To date, MIS surgery in children has demonstrated equivalence to open surgery with additional cost. The advantages of robotic surgery in children are harder to demonstrate than in adults since metrics used in the adult literature to show advantages do not always apply to children. The financial cost from loss of work productivity is more measurable than the impact of missed days of school. In addition, few have looked at the financial impact of a working parent having to stay at home to care for a postoperative child. Pain score assessments between open and MIS surgeries have not been rigorously tested as randomized trials looking at open versus robotic urologic surgeries in children are nonexistent. Formal multi-institutional prospective studies looking at matched open and RAL VUR patients are required.

The advantages for advancing robotics in children will be the greatest in residency education and patient-specific surgical simulation (Figure 5). With the aid of preoperative imaging, a surgeon or resident will be able to perform the surgery in a virtual reality arena prior to performing the surgery on the actual child. MIS surgery lends itself to task deconstruction better than open surgical procedures and we believe that in the era of surgical simulation training, robotic surgery will allow residents and novice roboticists to acquire technical competence in procedure performance more rapidly than open surgical procedures. The development of robotic surgery curricula will be necessary to achieve the highest level of patient outcomes.

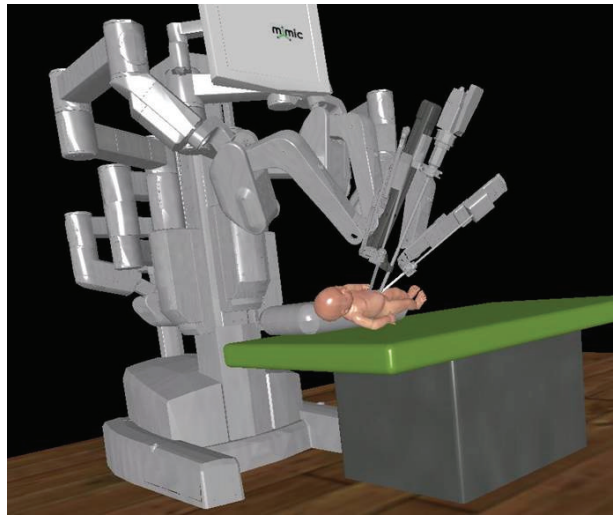

Figure 5: Patient-specific virtual reality robot docking simulation (Courtesy of MIMIC Technologies, Inc., Seattle, WA, USA).

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Review Article

Strengths and Pitfalls of Meta-Analysis Reports in Vesicoureteral Reflux

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There are many ongoing controversies surrounding vesicoureteral reflux (VUR). These include variable aspects of this common congenital anomaly. Lack of evidence-based recommendations has prolonged the debate. Systematic reviews (SRs) and meta-analysis (MA) are considered high-level evidence. The purpose of this review article is to summarize and critically appraise the available SR/MA pertaining to VUR. We also discuss the strength and pitfalls of SR/MA in general. A thorough literature search identified 9 SRs/MAs relevant to VUR. Both authors critically reviewed these articles for contents and methodological issues. There are many concerns about the quality of the studies included in these SRs. Clinical heterogeneity stemming from different patient selection criteria, interventions, and outcome definitions is a major issue. In spite of major advances in understanding different aspects of VUR in the last few decades, there is a paucity of randomized controlled trials in this field.

1. INTRODUCTION

Vesicoureteral reflux (VUR) is one of the most controversial topics in pediatric urology. The debate entails several aspects of VUR, such as clinical significance, diagnosis, treatment options and outcomes. The advent of endoscopic treatment of VUR has added to the complexity of this debate.

In an era of evidence-based medicine, there is a constant drive to use best available evidence in every day practice. Although systematic review (SR) and meta-analysis (MA) are well-established methods in generating evidence-based statements, they are not flawless. Specific steps should be taken to perform SRs, and clinical or statistical judgment calls are required of the authors. In addition, the quality of the available studies has a direct impact on the quality of SRs.

2. METHODS

In this review article, we first briefly explain the steps of a well-performed SR/MA [1] and then apply them to the topic of VUR. We did not intend to perform a systematic review of the topic but rather summarize and discuss the available SR/MA. Therefore, although we performed a thorough literature search, we did not use a conventional SR protocol. We included all the available SR/MA discussing any aspect of VUR (screening, diagnosis, or treatment). Both authors reviewed and critically appraised all articles.

What is a systematic review (SR) and meta-analysis (MA)?

SR is a method for secondary data analysis. In these types of studies, the authors attempt to identify all of the completed studies in relation to a specific research question in a systematic predefined manner. Then by using statistical methods, these results are combined to answer the research question based on all eligible studies. The actual statistical component of a systematic review is referred to as the MA.

Steps in SR/MA

(1) *The research question*: the cornerstone of an SR/MA must be a clear and specific question(s).

(2) *Definition of inclusion and exclusion criteria*: for example the authors may only include randomized controlled studies. Types of intervention(s), study

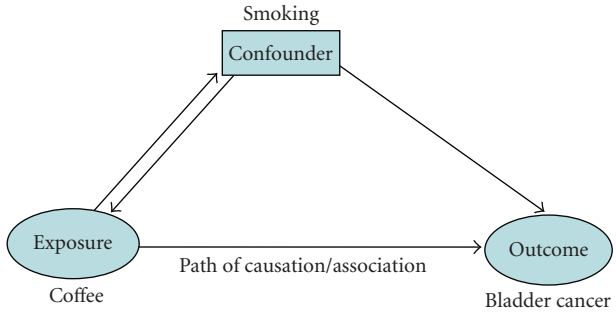

Figure 1: Confounder.

population(s), and outcomes of interest should all be clearly stated. At least two authors should assess studies eligibility.

(3) *Unbiased identification of all completed studies*: it is of paramount importance that a reproducible protocol be defined for the identification of studies. This includes a search of all available databases, a hand search of references and conference proceedings, and contact of experts in the field of interest. One common pitfall is to limit the search to few words or a single database such as MEDLINE. A medical librarian is an invaluable resource in developing effective search strategies.

(4) *Collection of data from each study*: standardized data collection forms are available and should be used to facilitate the subsequent analysis. Quality of the included studies is also assessed and recorded. There are multiple validated tools for this purpose. It is recommended that at least two authors collect the data independently.

(5) *Clear presentation of findings*: a summary of the results of literature search and reasons for exclusion of studies should be provided. Quality of the included studies should be discussed. The quality of reporting of meta-analyses (QUOROM) statement provides valuable guidelines for the authors [2].

(6) *The process of meta-analysis*

(a) Summary effect estimate and confidence interval. This is an average effect size, weighted by the size of the study. For example if the meta-analysis is combining the effect of a procedure versus antibiotics in preventing UTI, the final effect size is presented by a relative risk (RR). This is a weighted average size and describes a ratio between the incidence of UTI in two groups. The 95% confidence interval determines the statistical significance of the summary effect measure. If the interval is including 1 (RR = 1: equal incidence of UTI in the 2 groups), the findings are not statistically significant ($P > .05$).

(b) Heterogeneity: if the studies are too heterogeneous in terms of design, population, intervention or outcomes, they should not be combined. The authors must decide about this important issue based on their expertise and judgment. Combining these dissimilar studies will lead to clinical heterogeneity. There are statistical tests for assessing heterogeneity. If the P value of these tests is over 0.1, heterogeneity is unlikely, and combining the findings from the studies is reasonable. The P value of 0.1 is usually used instead of 0.05, to be less conservative in detecting heterogeneity. Forrest plot is a well-accepted graphic method to summarize the finding of M/A. It shows the effect size for each study and the whole analysis, along with the 95% CI. The results of the tests of heterogeneity and the sample size are usually presented as well.

(c) Assessment of publication bias: it is not unusual that small and negative studies are not published. An easy way to detect this bias is to generate a funnel plot. This is a scatter plot with the measure of effect and sample size on the X and Y axis, respectively. If publication bias is present the portion of the graph representing negative studies will be lacking.

(d) Subgroup and sensitivity analyses: in subgroup analysis the data from some subsets of studies are analyzed together (e.g., studies only looking at certain age groups are combined). In sensitivity analysis, the MA is done with and without certain studies to estimate their overall effects on the results.

The major shortcoming of an SR is that its quality is totally dependent on the quality of the included studies, the so-called "garbage in-garbage out" effect. This is a major issue when observational studies are analyzed. Confounders and bias are the two main pitfalls of these types of studies. Confounders are factors associated with both exposure and outcome that are not in the path of causation (see Figure 1). For example, if a cohort study determines coffee drinking is associated with bladder cancer, one could consider cigarette smoking as a confounder. Smokers may drink more coffee (association with exposure). In addition, smoking is a known risk factor for bladder cancer (association with the outcome). So any association between consuming coffee and bladder cancer could be entirely due to the confounding effect of smoking. Bias is a systematic error in selection of cases, measurement of outcome, or analysis of the data. There are statistical ways to minimize confounding and bias but the most effective method is to randomize the participants. Therefore, the quality of individual studies should be assessed carefully and taken into account when interpreting the overall results of an SR/MA.

3. RESULTS

Systematic reviews and meta-analysis for VUR:

A thorough search of available literature yields 9 SR/MA pertaining to VUR. In the following paragraphs, we critically appraise the findings of each paper.

Shanon and Feldman published a review article in 1990 evaluating the methodology of studies on different aspects of VUR [3]. The article by no means fulfills the criteria of a modern SR due the lack of a reproducible protocol. They identified four subsets of article addressing the following facets of VUR: diagnosis, treatment, association with hypertension, and end stage renal disease. They concluded that VCUG is the gold standard for diagnosis of VUR. The 4 then available articles about treatment did not show any advantage for surgery compared to medical treatment in terms of preventing UTIs or renal scarring. The authors also concluded that although there is a possible association between VUR and hypertension or end stage renal disease, because of the low quality of the literature, it could not be estimated quantitatively. Although the conclusions of this review are of limited value today, this publication is of importance since it was the first attempt to critically appraise the VUR literature.

In an SR/MA, Gordon et al. reviewed the literature to answer the question: "Does the presence of VUR predict renal damage in children admitted to hospital with urinary tract infection (UTI)?" [4]. The authors identified 12 studies after screening 838 publications which were extracted from 3 major electronic databases. Screened studies were excluded if more than 10% of data was missing or if they dealt with outpatients. Test of homogeneity revealed significant heterogeneity among the included studies. This is partly related to different patient populations and study protocols. Subgroup analysis was not performed. The authors concluded that the presence of VUR is a weak predictor of renal damage, since a positive voiding cysto-urethrogram (VCUG) only increased the chance of a positive DMSA renal scan by 20% and a negative VCUG reduced this chance by 8%.

Although this SR/MA utilized sound methodologies, there are some important shortcomings. Above all, the authors do not discuss the type and quality of the studies included. It is not clear to the reader if these studies were prospective or retrospective. Retrospective studies are prone to bias and confounding and generally are less valid. Exposure and outcome definitions may not be the same. For example how was the UTI diagnosed? what constitutes a positive DMSA scan? All these factors contribute to the significant heterogeneity and make the interpretation more difficult. In addition, the findings are not widely generalizable since this SR only included inpatients in an era when most UTIs are managed as outpatients.

Wheeler et al. published an SR/MA regarding antibiotics versus surgery for the treatment of VUR [5]. The authors only included randomized controlled trials (RCTs) which allowed the analysis of 8 studies involving 859 children. No significant difference was found in terms of renal scars and recurrence of a febrile UTI between the two groups. Nevertheless, children treated with surgical reimplantation had a 60% reduction in the risk of febrile UTI over a 5 year period of follow up. The authors concluded that it is uncertain whether identification and treatment of VUR confer any clinically important benefit. Although this was a well-performed study, many clinicians will disagree with the conclusions. In particular, a 60% reduction in the likelihood of febrile UTIs would likely be considered an important clinical achievement.

In an SR/MA on the effect of circumcision for prevention of UTI, Singh-Grewal and colleagues reviewed 12 studies including over 400 000 boys [6]. This included 1 RCT and 11 observational studies. The overall protective effect of circumcision was both clinically and statistically significant with an odds ratio of 0.13 ($P < .0001$). The effect was unaltered by study design. They estimated that in a general population, 111 circumcisions are required to prevent one UTI, due to a low incidence of UTI (1%). However, in certain subgroups of boys that are prone to UTI (such as those with VUR), the benefit of circumcision becomes more apparent. If the risk of recurrent UTI in patients with VUR is estimated to be between 10 and 30%, the number needed to treat will decrease to between 4 and 11.

This was a well-performed study without any major methodological flaws. Nonetheless, the quality of the included studies was variable. Methods of diagnosis of UTI were not uniform, follow ups were not similar and in some instances there was significant heterogeneity. Based on these findings, circumcision should be considered in the management of boys with VUR and UTI.

Elder and colleagues performed an MA on the success rate of endoscopic treatment of VUR [7]. They analyzed 63 publications encompassing 5527 patients and 8101 ureters. Only 3 studies were RCTs, with the rest being observational. All together, 5 different bulking agents were assessed, with only 6/63 (10%) of studies involving the use of Deflux, the most widely used agent today. They found out that the overall success rate of endoscopic treatment regardless of type agent used and grade of VUR is almost 75% with one injection. This can be improved to 85% with multiple treatments. High grade, neuropathic bladders, and duplicated ureters lowered the success rate. The reported rate of febrile UTI following treatment was less than 1% and cystitis occurred in 6% of cases. The paramount conclusion was that the success rate of endoscopic treatment approaches that of surgical reimplantation.

However, this study did not meet the standards for a well-done systematic review; the authors only interrogated the MEDLINE database plus a hand search of the references obtained as the basis for their literature search. An additional weakness is the possible heterogeneity of the studies in terms of their design, type of treatment, and length of followup. The authors did not address this issue by doing a test of heterogeneity.

Williams and colleagues performed an SR/MA to determine the efficacy of antibiotic prophylaxis for the prevention of UTI [8]. They included RCTs, comparing the effectiveness of antibiotics to each other or to placebo, in prevention

of UTIs in children. They analyzed 8 studies, and as a subset evaluated the effect of antibiotics in prevention of UTI in children with VUR. Only 2 studies reported the outcomes separately for patients with and without VUR. These studies showed a 54% reduction in subsequent positive urine cultures. The authors detected significant heterogeneity amongst the 8 included studies. Moreover, the above outcome is not considered clinically important since most pediatric urologists would not treat asymptomatic bacteriuria.

Venhola et al. performed a meta-analysis of the efficacy of medical versus surgical treatment of reflux [9]. They used recurrence of UTI, renal damage, and renal growth as the outcomes. They screened 639 studies and included only 5 of them in the final analysis. They found that the bulk of studies in the literature on VUR is retrospective and poorly designed. Their results and conclusions were very similar to the SR done by Wheeler 2 years earlier. In summary, they did not show any evidence of superiority of surgical treatment in preventing UTI, scars, or abnormal growth. This SR/MA has several shortcomings. The search strategy was suboptimal. The authors failed to identify at least another 4 trials that other authors have reported on. They combined the results of different study design types (RCT and cohort). The latter shortcoming is critical: the design of a study is so important that even if different types of studies reveal similar results, combining them may be misleading. Although mentioned in the article, they failed to emphasize a clinically important finding: the advantage of surgery over medical treatment in reduction in the likelihood of pyelonephritis.

Probably the most thorough SR in the VUR literature is a recent study by Hodson et al. from the Cochrane Renal Group [10]. This is an update of their SR on the treatment of VUR published in 2004. They performed an extensive and systematic literature review and identified 11 randomized controlled trials involving 1148 children. The RCTs included 7 comparing surgical (open or endoscopic) versus medical treatment, 2 compared prophylaxis antibiotics with surveillance and 2 compared different endoscopic methods. Although there were a few methodological issues with some of the RCTs (e.g., blinding of the outcome assessors, intention to treat analysis), the overall quality of the 11 included was acceptable. The authors found that the risk of any UTI is not different between surgically and medically treated groups. However, surgical correction of VUR results in a 50% reduction in febrile UTI (RR 0.54, 95% CI 0.32–0.92). With a 5 year incidence of febrile UTI estimated at 20%, the authors estimated that the number needed to treat to prevent one event was 9. In other words, 9 reimplantations would be required to prevent one episode of pyelonephritis over a 5 year period. New or progressive renal damage had a similar incidence in the two groups. In two small RCTs (total 143 children) with short followup, the likelihood of UTI was similar in patient on prophylactic antibiotics versus no treatment. In RCTs, looking at different types of bulking agents silicone (Macroplastique) and Deflux had similar results in terms of VUR correction rate and recurrent UTI. In a small study, GAX 35 collagen has been shown to be inferior to GAX 65 in correcting VUR. The authors concluded that it is uncertain that surgical treatment of VUR leads to clinically important benefit.

4. DISCUSSION

VUR has been at the centre of many debates in pediatric urology for several decades, going through several paradigm shifts. Up to the late 1970's and even the early 1980's, VUR was considered a significant disease and was treated primarily with a variety of open surgeries. Subsequently, large RCTs such as the International and Birmingham Reflux Studies [11, 12] cast a shadow of doubt on surgical intervention as the management of first choice. These seminal studies were based on several assumptions:

(1) VUR is a pathologic finding;

(2) VUR facilitates UTI;

(3) renal parenchymal infection may cause renal damage, hypertension, and renal insufficiency;

(4) correction of reflux by surgery, or prevention of UTI with antibiotic prophylaxis until spontaneous resolution, prevents these unfavorable outcomes.

This resulted in failure of including another management strategy in these large studies, namely clinical surveillance. Nevertheless, a new perspective was generated: VUR can be managed medically and only selected patients will require surgery. These initial randomized studies also showed that surgical treatment reduces the likelihood of febrile UTI. Some authors would question the importance of this outcome without demonstrating a concomitant reduction in renal damage. However, one should not ignore the potential morbidity and even rare mortality associated with febrile UTI, especially in young children.

More recent findings have changed the landscape again. The fact that up to 50% of radiological renal defects could be congenital and not a consequence of UTI implies that VUR may be even less clinically important [13]. Studies have persistently failed to show a beneficial effect for treatment of VUR in reducing the risk of renal scarring, even when the incidence of febrile UTI is decreased.

The efficacy and safety of long-term antibiotics have also been questioned. A recent RCT by Garin et al. did not demonstrate any benefit from antibiotic versus surveillance in reducing febrile UTI in children with low and moderate grade VUR after one year of followup [14]. In addition long-term antibiotics may not be as harmless as we once thought [15, 16].

Another major advance is the introduction of a safe and effective bulking agent for endoscopic treatment of VUR, that is, Deflux. However, this method has never been compared to other management strategies in a prospective manner. Again our assumptions have preceded the evidence in adopting a treatment strategy.

Management of VUR also influences other important clinical decisions, such as when to image children with febrile UTI or siblings of patients with VUR [17]. Finally, the cost effectiveness and impact on quality of life for these

investigations and treatments have not been assessed in prospective fashion.

We believe pediatric urologists should spearhead efforts to generate the high-level evidence guiding the management of VUR. The best way is to compare all the available strategies in a randomized controlled trial. Ideally, all important outcomes should be evaluated with adequate followup. This requires recruitment of several hundreds patients, randomizing them into 3 groups (surveillance, antibiotics, surgery) and following them for 4-5 years. Only with such a design will questions about recurrence of UTI and renal damage ever be answered. In addition effects of potential confounders such as sex, grade of VUR, mode of presentation and dysfunctional voiding can be evaluated. This will also provide an opportunity to compare the cost–benefit of each strategy.

Another major benefit of this ideal study is a better clarification of the magnitude of the clinical importance of VUR. For example, if surveillance is shown to be an acceptable long-term management, there is no reason to diagnose VUR, because it would not change our clinical approach. On the other hand, if active treatment is associated with a better outcome, one can conclude that VUR is a clinically significant phenomenon that requires diagnosis.

There are many barriers to performing an ideal RCT in children, especially those involving a surgical arm. Randomization between several divergent modalities is usually met with low parental acceptance. The requirement for a large sample size combined with long-term followup will considerably increase the cost, probably to millions of dollars. It is very difficult if not impossible to perform this type of studies in a single centre. Multicentre trials are inherently more expensive and difficult to run. Ethical issues may also impede the recruitment [18].

In spite of all the adversities, a few RCTs are underway to answer the above questions [19].

5. CONCLUSIONS

The quality of available studies regarding VUR is highly variable and in many cases suboptimal. Recent findings and advances in different aspects of VUR mandate a new look into our clinical management of this disorder. Ideally, a large multicentre randomized controlled trial should be done, including all available management strategies.

ABBREVIATIONS

95% CI:	95% Confidence interval
DMSA:	Dimercaptosuccinic acid
MA:	Meta-analysis
QUOROM:	Quality of reporting of meta-analysis
RCT:	Randomized controlled trial
RR:	Relative risk
SR:	Systematic review
UTI:	Urinary tact infection
VCUG:	Voiding cysto-urethrogram
VUR:	Vesicoureteral reflux

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