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Controversies in the Management of Vesicoureteral Reflux

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Abstract Vesicoureteral reflux (VUR) is the abnormal retrograde flow of urine from the bladder into the upper urinary tract. Diagnosis and subsequent management of VUR have become increasingly controversial, with differing opinions over which children should be evaluated for reflux, and when detected, who should undergo treatment. Management goals include prevention of recurrent febrile urinary tract infection (fUTI) and renal injury while minimizing the morbidity of treatment and follow-up. Management options include observation with or without continuous antibiotic prophylaxis and surgical correction via endoscopic, open or laparoscopic/robotic approaches. Management should be individualized and based on patient age, health, risk of subsequent renal injury, clinical course, renal function, and parental preference.

Keywords Vesicoureteral reflux · Voiding cystourethrogram · Febrile urinary tract infection · Pyelonephritis · Hydronephrosis · Antibiotic prophylaxis

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Introduction

Vesicoureteral reflux (VUR) is one of the most common urologic diagnoses affecting children, with an estimated prevalence of 0.4–1.8 % in the general pediatric population and 30 % in those with a history of febrile urinary tract infection (fUTI) [1, 2]. UTI is the most common bacterial infection in childhood, and the potential for significant morbidity has placed emphasis on early and accurate diagnosis as well as appropriate antibiotic therapy [3, 4]. Dilation of the upper urinary tract as noted on prenatal ultrasound may also be suggestive of VUR; numerous studies have demonstrated that reflux occurs in 10–20 % of children with antenatally detected hydronephrosis [5].

Primary VUR results from failure of the ureterovesical junction (UVJ) to develop or function properly and is frequently associated with an abnormally short intramural tunnel. Spontaneous resolution of primary reflux is common. The exact mechanism of spontaneous resolution has yet to be elucidated, but it is hypothesized to be a multifactorial process related to remodeling of the UVJ, elongation of intravesical ureter, and stabilization of bladder voiding dynamics. The likelihood of resolution is associated with the grade of reflux, gender, age, voiding dysfunction, presence of renal scarring, and bladder volume at the onset of VUR on voiding cystourethrogram (VCUG). Several studies have now demonstrated that administration of low-dose antibiotics in children with VUR prevents recurrent of UTIs, especially in those with dilating grades of VUR. The need for surgical correction is dictated by a particular child's risk for further infections, risk for renal scarring and chronic kidney disease, likelihood of spontaneous resolution, and parental preferences. Various online calculators exist to predict reflux resolution (Fig. 1) [6]. An individualized risk-based approach that takes into

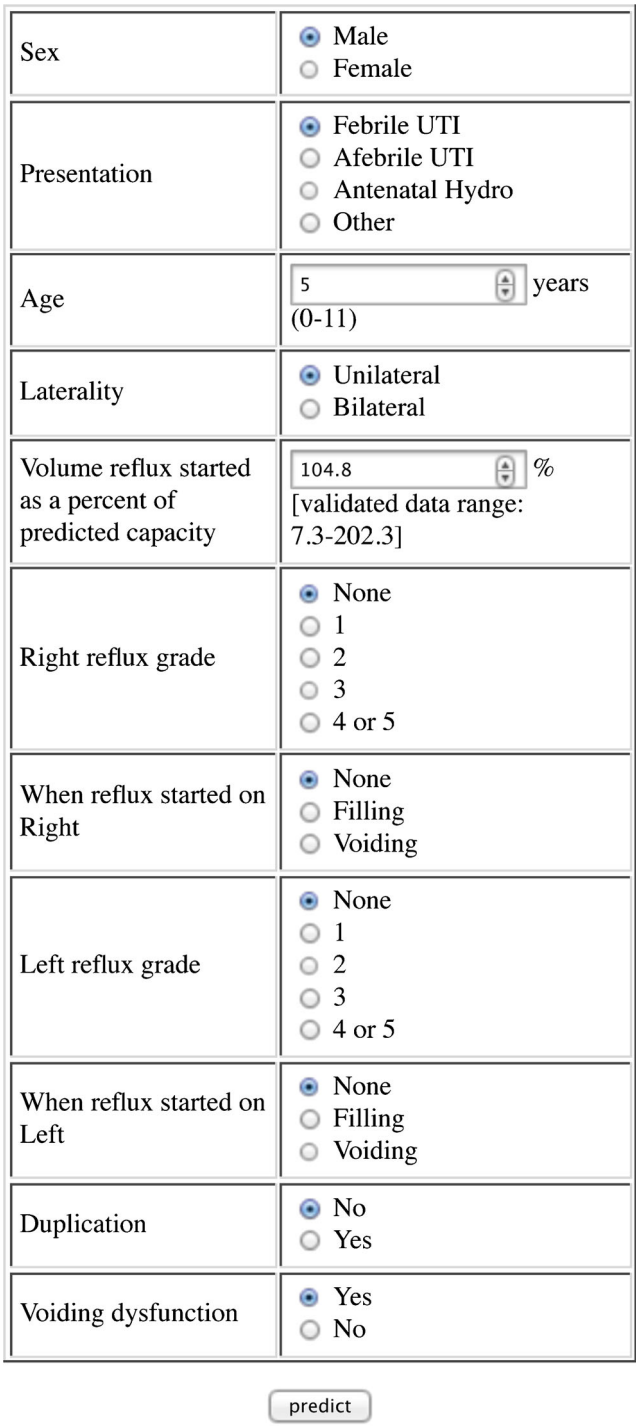

Fig. 1 Neural network is a computational model that incorporates multiple variables allowing for improved individualized prediction of vesicoureteral reflux resolution. Available at: http://godot.urol.uic.edu/urocomp/SVM_model_revised.html

consideration a multitude of demographic, radiographic, and clinical factors should guide management [7–9]; however, a universal management algorithm is lacking, and controversies abound regarding both diagnosis and treatment of primary reflux.

When is VCUG Indicated?

The detection of VUR often follows the diagnosis of febrile UTI. In a febrile child, the diagnosis of a UTI requires a positive urine culture. The method of obtaining the urine specimen is critical for an accurate diagnosis of UTI. Urine specimens should be obtained through catheterization or suprapubic aspiration if a clean catch specimen is not feasible, as the diagnosis of UTI cannot be reliably established via urine culture collected in a bag. In 2011, the American Academy of Pediatrics (AAP) revised their practice parameters regarding the diagnosis and management of initial fUTIs in infants and young children aged 2 to 24 months [10]. To accurately establish the diagnosis of UTI, the AAP requires the presence of >50,000 colony-forming unites per milliliter of uropathogen on catheterized specimen as well as pyuria and/or bacteriuria on urinalysis [10]. This value is less than other guidelines that require >100,000 CFU but that do not require pyuria. The AAP guidelines also recommend that infants with initial fUTI undergo a renal-bladder ultrasound (RBUS), but state that VCUG should not be routinely performed unless indicated by sonographic findings (i.e., hydronephrosis and scarring). Several recent publications focusing on the utility of RBUS as a diagnostic tool in children with fUTI have reinforced the previously well-known fact that sonography is a poor screening test for VUR [11–13]. Many children with VUR, and even high grade VUR, will have a normal renal ultrasound. This calls into question the AAP recommendation to use sonographic findings as the determinant for obtaining a VCUG. While most clinicians agree with the majority of action statements described in the AAP guidelines, the diagnostic imaging recommendations in young infants and children are widely debated [7, 14].

The section on urology of the AAP expressed strong opposition to the AAP guidelines with respect to the omission of a recommended VCUG after an initial fUTI. Failure to effectively screen fUTI may place young children with VUR at risk for failure to diagnose and appropriately manage VUR. The clinical benefit of treating reflux has been reaffirmed by two recently published large, multi-institutional studies [15••, 16••]. The RIVUR Trial, a 2-year, multi-institutional, randomized, placebo-controlled study involving 607 children with VUR recently proved that antimicrobial prophylaxis substantially reduced the risk of recurrent UTIs [15••]. Similarly, the Swedish Reflux Study demonstrated benefit of prophylactic antibiotics and endoscopic injection in reducing recurrent pyelonephritis and new renal scarring in a group of 1-year-old children with dilating VUR [16••]. If VCUG is deferred following initial fUTI, families must be counseled regarding the risks and benefits of imaging for diagnosis and management of VUR, as well as the need to minimize the chance of renal injury by rapid diagnosis and treatment of subsequent UTIs.

The role of VCUG in children with antenatal hydronephrosis also remains a source of controversy. Currently, there is no clear evidence to support or avoid postnatal imaging for VUR in this cohort. It remains unproven whether the identification and treatment of children diagnosed with VUR as part of antenatal hydronephrosis evaluation confers any clinical benefit [5, 17]. A recently published consensus statement suggests that a VCUG is an option for all children with antenatal dilation of the urinary tract and is indicated in children with more severe dilation or other abnormalities [18•].

Who Benefits from Antibiotic Prophylaxis?

The use of prophylactic antibiotics may be considered a non-specific approach to the prevention of recurrent UTIs. Antibiotic prophylaxis in children with VUR has been widely employed, and the reduction in UTIs in those children receiving prophylaxis has been confirmed by the RIVUR and Swedish Reflux trials [15••, 16••]. Daily administration of low-dose antibiotics is based on the knowledge that new reflux-associated renal scarring appears to occur exclusively in the setting of infected urine and that most children will spontaneously resolve VUR. The maintenance of sterile urine until spontaneous resolution may avoid the morbidity associated with surgical intervention as well as renal parenchymal scarring. While continuous antibiotic prophylaxis is considered safe and well tolerated in general, the emergence of bacteria with high rates of resistance has been reported [19]. In the RIVUR Trial, children on prophylaxis were significantly more likely to experience recurrent infections caused by a resistant pathogen [15••].

Neither the revised AAP guidelines nor the NICE guidelines recommend routinely prescribing prophylactic antibiotics in infants and children following their first UTI [10, 20]. As might be expected, the benefit of prophylactic antibiotics is more easily demonstrated when used in specific populations known to be at high risk for recurrent UTI [16••, 21]. Clinicians and parents often opt for intervention based on likelihood of spontaneous resolution as well as clinical course, thus placing an emphasis on the ability to predict the likelihood of recurrent febrile infections. Dilating reflux, renal scarring, bladder-bowel dysfunction, and VUR that occurs at low bladder volumes are all associated with breakthrough infections [22, 23•, 24]. Several studies suggest that children on antibiotic prophylaxis without breakthrough infections or evidence of renal injury can be safely observed without antibiotic prophylaxis or correction of VUR, once they have reached an age and developed bowel and bladder habits when urinary tract infections are less likely [25–27]. Others would only consider this option in boys or in girls with lower grades of VUR.

Who Benefits from Surgical Correction of Vesicoureteral Reflux?

While there is a natural tendency for reflux to improve or cease with time, there remains a subset of children with persistent VUR who are at risk for recurrent pyelonephritis and potential sequela from renal injury. Pyelonephritis, with or without documented VUR, can lead to renal scarring and subsequent complications such as hypertension, proteinuria, and chronic kidney disease [28, 29]. Thus, the key focus in selecting patients for surgical correction should be identifying those unlikely to resolve VUR and those at greatest risk for recurrent pyelonephritis. It is well documented that high-grade reflux is associated with increased risk of renal scarring as well as lower resolution rates [8, 16••, 30–32]. Bladder volume at which reflux occurs during VCUG has also been shown to affect the likelihood of spontaneous resolution independent of VUR grade. Reflux that only occurs at greater bladder volumes or during voiding has improved resolution rates [33]. In addition, VUR that occurs at lower bladder volume has been shown to be an independent risk factor for breakthrough fUTI [23•].

Surgical intervention may be necessary in children with persistent reflux, renal scarring, or recurrent fUTI. Both open and endoscopic approaches to reflux correction may be successful in correcting reflux and have been shown to reduce the incidence of fUTIs. The 2010 AUA Guidelines recommend management of any suspected bladder-bowel dysfunction, preferably prior to any surgical intervention [7]. Persistent bladder-bowel dysfunction is not only associated with increased risk of fUTI but also associated with increased surgical complications and failure rates.

Role of Endoscopic Therapy

Endoscopic correction of VUR using a bulking agent was initially described as an alternative to continuous antibiotic prophylaxis or ureteral reimplantation in 1981; O'Donnell and Puri advanced the concept by performing subureteric injections using Teflon paste coining the term "STING" (subureteric teflon injection) [34]. In 2001, the United States Food and Drug Administration approved the use of dextranomer hyaluronic acid co-polymer (Dx/HA; Deflux® Salix Pharmaceuticals Inc., Raleigh, NC) for endoscopic injection in pediatric patients with primary VUR grades II–IV. Modifications led to the development of the double hydrodistention implantation technique (Double HIT), where total ureteral tunnel and orifice coaptation is achieved by two intramural injections [35, 36]. Proponents of the endoscopic approach note the benefits compared to ureteral reimplantation include outpatient surgery and decreased patient morbidity [24]. Opponents of endoscopic treatment note higher initial

failure rates and recurrence rates compared to ureteral reimplantation.

Because of the minimally invasive nature of Dx/HA injection, the initial frequency of endoscopic management of VUR increased rapidly [37, 38]. Reported initial efficacy rates, while up to 94 % with the double HIT method [39–41], are known to vary widely between surgeons and techniques [42]. The literature indicates that endoscopic injection is relatively effective for the treatment of most VUR, while emphasizing the importance of reflux grade and structural/functional bladder anomalies on ultimate success rates. In a systematic meta-analysis evaluating endoscopic treatment of pediatric VUR, the estimated success rate for endoscopic therapy after a single injection was 78 % for grades I and II, 72 % for grade III, 63 % for IV, and 50 % for grade V VUR [43]. Recurrence rates of VUR after initial success with endoscopic injection appear to be around 15–20 % within several years [15••].

Due to the lower success rates compared to open ureteral reimplantation, the AUA Reflux Guidelines recommend postoperative VCUG following endoscopic correction of VUR [7]. Others have suggested that postoperative imaging should be reflective of the surgeon's experience. It has been reported that at least 20 cases are required to achieve sufficient proficiency with endoscopic repair of VUR, and therefore, inexperienced surgeons should routinely obtain postoperative VCUG to ascertain radiographic success [35]. It is unclear if routine long-term follow-up VCUGs should be obtained in those that underwent endoscopic correction. Given the higher failure and recurrence rate with endoscopic treatment of VUR, it seems prudent to obtain a VCUG in those that develop recurrent fUTI [41]. As with open operative correction of VUR, there is a risk of asymptomatic ureteral obstruction with endoscopic treatment [44]. A renal-bladder ultrasound at 6 weeks and 1 year should be considered to screen for both acute and chronic asymptomatic ureteral obstruction.

Role of Robot-Assisted Laparoscopic Ureteral Reimplantation

Laparoscopic approaches to ureteral reimplantation were initially reported in the 1990s [45–47]. More recently, robot-assisted laparoscopic approaches have been described, negating some of the longer operative times and greater technical difficulty associated with pure laparoscopy [48, 49]. Even with robot assistance, a learning curve has been demonstrated with this technique similar to other robotic-assisted laparoscopic techniques in terms of operative time. While open surgery remains the gold standard for the correction of vesicoureteral reflux, robot-assisted laparoscopic reconstructive surgeries in the pediatric population have gained increasing acceptance [50, 51]. Several series have documented the safety and efficacy of extravesical robot reimplantation in children; typically, operative times are longer but length of stay and narcotic use are reduced compared to open ureteroneocystostomy [49–53].

In some series, success rates are comparable to open reimplantation [49, 52] but other authors report significantly lower cure rates (77–92.3 %) than that routinely achieved with open repair [54–56]. Intravesical robot-assisted ureteral reimplantation has also been reported, however, its use remains more limited due to technical difficulties including maintenance of pneumovesicum, trocar placement, and difficulty navigating robotic instruments in small-capacity bladders [50]. However, proponents of this intravesical approach note it the advantage of keeping the operation extraperitoneal and replicating the gold-standard open ureteral reimplantation technique. As with other robotic-assisted laparoscopic operations, advantages compared to an open approach seem most apparent in older children. Long-term studies demonstrating comparable efficacy, cost, and improved quality of life benefits of robotic surgery over standard open repairs will be required before there is widespread adoption of this technique.

Need for Long-Term Follow-up?

While the incidence of significant comorbidities in children with VUR is often minimal at diagnosis, long-term follow-up with respect to disease-specific morbidity is necessary as decades may pass between the first renal-scaring pyelonephritis and development of hypertension or end-stage renal disease [57]. Children with VUR should undergo annual blood pressure monitoring, height, and weight assessment, as well as urinalysis for proteinuria/bacteriuria, with a culture if infection is suspected. Renal ultrasound has been recommended annually to monitor renal growth [7], however, since most children with normal renal function at the time of VUR diagnosis will do well in the long term others suggest a more selective approach to radiographic follow-up for children with a history of VUR. In those with extensive kidney damage, especially when bilateral, monitoring should include frequent blood pressure measurement and excretory function assessment [58].

Conclusions

Controversy persists regarding the diagnosis and optimal management of vesicoureteral reflux in the pediatric population. Management of VUR should be individualized and focused on the goals of preventing recurrent UTI and renal injury as well as minimizing morbidity of treatment and follow-up.

Compliance with Ethics Guidelines

Conflict of Interest Angela M. Arlen and Christopher S. Cooper declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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