Evaluation and Management of Vesicoureteral Reflux: A Decade of Change

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Vesicoureteral reflux (VUR) is the most common urinary tract abnormality in children,[1] yet the optimal diagnostic and therapeutic approach remains controversial. Studies over the past decade have raised significant questions regarding all aspects of VUR management, including the approach to the evaluation of childhood **urinary tract infection (UTI).** Determining which children will actually benefit from diagnosis and treatment is the greatest challenge to VUR management.

Definition, Etiology, and Incidence

VUR, the retrograde flow of urine from the bladder up the ureter toward the kidney, is the result of an incompetent antireflux mechanism at the **ureterovesical junction (UVJ).** VUR is considered primary or secondary depending on the main etiology. Primary VUR, the most common, is caused by a congenital maldevelopment of the UVJ antireflux mechanism.[2] Secondary VUR results when abnormally increased bladder pressures, as seen in posterior urethral valves, neuropathic bladder, or voiding dysfunction, overwhelm and/or destabilize the normal UVJ.[3]

VUR is estimated to occur in ~1-3% of otherwise healthy children. In children with a febrile UTI, the incidence increases to ~30-40% and there is a female predominance of ~4:1.[1] Nearly 80% of VUR cases are diagnosed after UTI.[3] Approximately 10-20% of infants with a history of prenatal hydronephrosis have VUR.[4] A strong inheritance pattern exists for primary VUR, with an incidence of ~32% in siblings[5] and ~65% in offspring of a patient with a history of VUR.[6]

Reflux Nephropathy

The clinical significance of VUR is its association with renal parenchymal scarring, also referred to as **reflux nephropathy (RN).**[7] Historically, RN was postulated to be due to a "water-hammer" effect, resulting from the direct transmission of bladder pressures to the renal pelvis via sterile refluxing urine.[8] While VUR associated with abnormally elevated bladder pressures may cause renal damage, in 1975 Ransley and Risdon demonstrated that, at physiologic bladder pressures, renal scarring occurs only in the presence of UTI.[9] In the presence of UTI, reflux facilitates the transport of infected urine from the bladder to the kidney, potentially leading to bacterial invasion of the renal parenchyma (i.e., pyelonephritis). The inflammatory response, in turn, leads to focal ischemia, interstitial damage, fibrosis, and potentially irreversible renal scarring.[10]

The primary concern regarding RN is the potential for serious long-term sequelae, including hypertension, chronic kidney disease, and end-stage renal disease. The risk of developing such complications may vary with age, degree of renal scarring, and unilaterality/bilaterality of damage.[11] Retrospective studies have demonstrated that the incidence of hypertension in the setting of RN is ~15-20% in children, but ~30-40% in adults.[12] In the United States and Canada in 2008, RN was the fourth leading diagnosis in pediatric transplant (5.2%), dialysis (3.5%), and chronic kidney disease (8.5%) patients, and, in Italy, VUR remains a leading cause of end-stage renal disease in children and young adults, accounting for 25% of all cases.[11] Few prospective, longitudinal studies of RN-associated complications exist; thus, clear incidences and actual risks of the late clinical sequelae remain poorly defined.

Historical Approach to Evaluation and Treatment

The American Academy of Pediatrics recommends both renal **ultrasonography (US)** and **voiding cystourethrography (VCUG)** following first febrile UTI in all children between 2 months and 2 years of age, as the prevalence of VUR and risk of renal scarring following pyelonephritis is highest in this age group.[1] US is a safe, noninvasive, highly sensitive screening test for collecting system dilatation. However, because its sensitivity for detecting VUR or renal scarring is low, it should primarily be regarded as a screening tool to detect patients at risk of these or other abnormalities.[11] The traditional gold standard diagnostic study for detecting VUR is fluoroscopic VCUG, in which contrast material is instilled into the bladder through a catheter, and intermittent fluoroscopy is utilized during filling and voiding. VCUG allows for both visualization of urethral and bladder anatomy, as well as grading of VUR severity if present.[13]

The initial grade of VUR is correlated with both the likelihood of spontaneous reflux resolution as well as the risk of renal scarring.[1] Grades I and II VUR, non-dilating "low-grade" reflux, are found in over half of children diagnosed with VUR after UTI, and, regardless of age at presentation, spontaneously resolves within 5 years in 92% and 81%, respectively.[14] In contrast, grades IV and V, "high-grade" reflux, involve moderate (IV) to severe (V) dilation of the collecting system, blunting of the calyces, and tortuosity of the ureter,[15] and are unlikely to spontaneously resolve.[14]

VCUG requires urethral catheterization, in most cases of the non-sedated child, and ionizing radiation exposure. Direct **radionuclide cystography (RNC)** is an alternative to VCUG in which a radionuclide, rather than contrast material, is instilled into the bladder under a gamma camera detector. RNC involves 100 times less ionizing radiation than traditional VCUG and is highly sensitive for detecting VUR; however, it does not allow for anatomical assessment or precise VUR grading, and still requires catheterization.[13] Thus RNC is not recommended as the initial diagnostic study in a child with suspected VUR, but may be used in follow-up studies.[1]

The primary goal of VUR treatment is prevention of reflux-related febrile UTIs to reduce the risk of renal scarring and long-term consequences.[14] Historically, the initial approach to VUR man-

agement was via open surgical correction of the UVJ abnormality, "ureteral reimplantation," performed using either an intravesical, extravesical, or combined approach.[2] Intravesical approaches have a 98-100% success rate; however, these procedures are associated with transient postoperative hematuria and bladder spasm. In contrast, extravesical approaches have similar success rates, but avoid opening the bladder, and thus, are associated with less postoperative morbidity. However, due to an increased risk of acute urinary retention after bilateral extravesical procedures, this approach is more commonly performed in children with unilateral VUR.[16]

In 1979 Smellie et al.[17] challenged the concept that surgery is necessary in all children with VUR. Their seminal study demonstrated the role of medical therapy via continuous low-dose antibiotic prophylaxis in reducing the rate of UTI while awaiting reflux resolution or surgical correction. This led to widely divergent opinions regarding the optimal initial management of VUR, and two **randomized, controlled trials (RCTs)**, the International Reflux Study[18] and the Birmingham Study,[19] compared the outcome of surgical versus medical treatment of grade III-IV VUR. A 50% decrease in the incidence of clinical pyelonephritis in the surgical group was noted;[18] however, there were no differences in the incidence of cystitis or renal scars between the two management arms.[18, 19]

Based on these findings and the high resolution rates in low-grade reflux, in 1997 the American Urological Association recommended the initial management of children with grades I-IV VUR consist of antibiotic prophylaxis until either spontaneous reflux resolution, or surgery is indicated. Indications for surgical correction included: (1) recurrent UTIs despite prophylaxis (i.e., breakthrough UTIs); (2) persistent VUR after a variable period of observation; (3) poor compliance with prophylaxis; and (4) development of new renal scarring.[14] A relative indication for surgery is if the parents are felt to be unreliable in terms of seeking treatment immediately at the first sign of infection, and thus, placing the child at risk for pyelonephritis and renal scarring.

Technetium-99m labeled **dimercaptosuccinic acid scintigraphy (DMSA scan)** is the gold standard technique for the detection and evaluation of acute pyelonephritis and renal scarring. When performed at the time of UTI, sensitivity and specificity for detecting pyelonephritis are both 92-95%,[20] and, when performed at 6-month follow-up, are 96% and 98%, respectively, for detection of renal scarring.[21] Although follow-up DMSA scan may help identify those at risk for long-term sequelae, its routine use is controversial, as the incidence of scarring after first febrile UTI is only ~15%.[22]

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Changes in Evaluation

Until recently a common assumption was that VUR is an absolute prerequisite for new or acquired renal scarring following UTI; however, over the past decade this assumption has been questioned. DMSA scintigraphy has demonstrated that pyelonephritis, rather than VUR, is the prerequisite for acquired renal scarring,[21] and that low-grade VUR is of low clinical significance.[23, 24] Evidence supporting these conclusions include: (1) only about two-thirds of children with a febrile UTI actually have acute pyelonephritis, and only about one-third of those have VUR;[23] (2) there is no significant difference in the risk of pyelonephritis or acquired renal scarring between children with low-grade VUR and those without VUR, whereas children with high-grade VUR have a significantly increased risk of pyelonephritis as well as renal scarring;[23] and (3) once pyelonephritis occurs, the rate of subsequent renal scarring (~30-60%)[23, 25] is independent of the presence of reflux; children without pyelonephritis are not at risk for scarring, regardless of the presence of reflux.[21, 26]

Recently, a new diagnostic strategy for the evaluation of childhood UTI, the **"top-down" approach (TDA)**, has been proposed.[27] In contrast to the traditional "bottom-up" approach, in which the initial diagnostic concern is detection of VUR via VCUG, the TDA focuses first on detecting pyelonephritis via a DMSA scan performed at the time of infection.[28] Since children with pyelonephritis are more likely to have high-grade VUR, the TDA recommends a VCUG be performed only in those with an abnormal DMSA.[27]

Both retrospective and prospective studies have confirmed the validity of the TDA. Hansson et al.[29] and Preda et al.[30] found that the sensitivity and negative predictive value (NPV) of initial DMSA scan after febrile UTI to predict VUR were 73% and 87%, respectively. The incidence of VUR missed with this strategy was ~10%, all of which were low-grade, and both the sensitivity and NPV of DMSA to predict high-grade VUR were 100%. Thus, if VCUG is only performed in those children with DMSA-confirmed pyelonephritis, then *all* cases of clinically significant high-grade VUR would be detected and ~40% of VCUGs could be avoided.[27]

Changes in Management

Increasing concerns regarding antibiotic-resistant bacteria, poor patient compliance with prophylaxis (reported to be as low as 40%[31]), and recent challenges to the clinical benefit of prophylaxis have questioned the role of antibiotic prophylaxis as the initial management in all VUR patients.[32] A major limitation of prior RCTs was the lack of a placebo or "observation-only" arm with which to compare the efficacy of antibiotic prophylaxis; however, four recently published RCTs, all of which included a control group,[24, 33-35] failed to demonstrate a reduction in the rate of UTI in children with low-grade reflux treated with prophylaxis. As these studies were limited by insufficient statistical power, enrollment primarily of children with grades I-III VUR, and lack of categorization regarding voiding patterns, the question remains whether antibiotic prophylaxis is indeed an effective treatment for reflux, particularly in children with grades III-V.

Despite the high success rate of antireflux surgery, concerns regarding the invasive nature and morbidity of these procedures have led to less invasive alternatives for VUR correction.[36] Both intra-

vesical and extravesical procedures have been approached laparoscopically, which offers the benefits of improved cosmesis due to smaller incision(s), shorter hospital stay, and decreased postoperative bladder spasm and analgesia requirements.[37] Although success rates are comparable to open surgical correction,[38] a steep learning curve, increased postoperative complications, and increased operating time have led few to embrace the laparoscopic approach.

In 2001, dextanomer/hyaluronic acid (Dx/HA) (Deflux®, [Oceana Therapeutics Ltd, USA]) was approved as an injectable gel for endoscopic correction of grades II-IV VUR. Comprised of cystoscopy and subureteric injection of Dx/HA under general anesthesia, endoscopic treatment is a minimally invasive outpatient procedure, generally lasting less than 20 minutes, and the child may resume preoperative activities immediately after. The likelihood of initial success after Dx/HA injection, in terms of VUR resolution, is correlated with preoperative VUR grade.[39] On average, success rates for low-grade reflux are ~85%, and ~75% and ~60% for grade III and IV, respectively.[40] The long-term durability of Dx/HA is unclear, with long-term success rates ranging from 74-87% after 1-5 years.[41] Nevertheless, some have begun to recommend it as a first-line treatment alternative to prophylaxis or surgery.[39] In the absence of rigorous comparisons between the different treatment modalities, however, the indications for endoscopic treatment should currently remain the same as open surgery.[14]

Over the past decade, the evaluation of childhood UTI and nearly all aspects of VUR management have experienced a large paradigm shift. In some centers, the initial diagnostic study in children presenting with febrile UTI has changed from VCUG for detection of VUR to DMSA scan to assess for pyelonephritis. Under this new "top-down" approach, a VCUG is only ordered in those with DMSA-confirmed pyelonephritis. Antibiotic prophylaxis is currently the mainstay of initial VUR management, with surgical correction being reserved for select cases. Traditional viewpoints regarding the clinical significance of low-grade VUR as well as its management with prophylactic antibiotics have also recently been challenged. Many authorities now consider low-grade VUR clinically insignificant, and recent RCTs strongly suggest that antibiotic prophylaxis is ineffective at reducing the rate of febrile UTI in low-grade VUR. Given the unclear effectiveness of antibiotic prophylaxis, a long-term, multicenter, double-blind, randomized, placebo-controlled trial was designed in 2005 and is currently underway: the **Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR)** study. This large trial of 600 children should have the necessary statistical power to assess the efficacy of antibiotics in reducing the rate of febrile UTI and renal scarring.[42]

In the meantime, the recently published results from the Swedish Reflux Study, a prospective, multicenter RCT, have addressed some of the questions regarding the management of grade III-IV reflux. In this study, 203 children between the ages of 1 and 2 years with grade III-IV VUR were randomized to treatment with either antibiotic prophylaxis, endoscopic treatment with Dx/HA, or surveillance with antibiotics only for symptomatic UTI.[32] After 2 years of follow-up they demonstrated: (1) reflux resolution or downgrading to low-grade was significantly more common in the endoscopic group (~70%) compared to the prophylaxis and surveillance groups (~40-45%); (2) recurrent dilating reflux occurred in 20% of those initially treated successfully with Dx/HA; (3) when compared to the control group, prophylaxis and endoscopic treatment both decreased the rate of recurrent febrile UTI in females by ~60%; neither treatment reduced the rate of febrile UTI in males; and (4) the rate of new scarring in females was significantly less in the prophylaxis group compared to the control group, whereas in males the rate of new scarring was low in all groups.[43-45] While these results must be validated, hopefully by the RIVUR study, this is the largest RCT to date investigating children with dilating reflux, and the first to provide convincing evidence that antibiotic prophylaxis is effective in reducing the rate of febrile UTI and renal scarring in children with dilating reflux, albeit only in females.

Conclusion

The evaluation and management of VUR is evolving. The historical philosophy of evaluating for VUR in all children presenting with UTI and managing all children with VUR with antibiotic prophylaxis or surgical correction has evolved to identifying those children at greatest risk for renal scarring via the use of DMSA scintigraphy and the "top-down" approach. Endoscopic treatment has emerged as a new promising management option and results of the RIVUR study are likely to lead to further modification of VUR management in the coming decade.

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