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Vesicoureteral Reflux: Special Considerations and Specific Populations

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Abstract

Purpose of Review This review will hopefully serve as a brief update on the current approaches to vesicoureteral reflux (VUR) within the context of historical approaches to this disorder and dispelling some of the myths surrounding its treatment. There is also greater focus on certain populations with VUR that may (or may not) be at particular risk.

Recent Findings Despite several large studies showing the benefit of antibiotic prophylaxis in preventing infections in VUR, there continues to be conflicting results in smaller scale studies or in regard to renal scarring that prevent its accepted use universally. Some of these conflicting results are a product of comparing a mixed population of individuals, as there are certain populations that seem to benefit from antibiotic prophylaxis and for which it should be considered. Similarly, surgical correction of VUR is not beneficial for many individuals even within certain higher risk populations, such as higher grade VUR, pre-pubertal females, and renal transplant recipients.

Summary Preceding febrile infections and the presence of renal scarring are two indicators of higher risk individuals. However, renal scarring in some individuals may not be secondary to infections. Therefore, an individualized approach to each patient with VUR is needed, with some needing treatment by surgery, some needing antibiotic prophylaxis, some needing optimal bladder care, and even others needing treatment of the sequelae of renal scarring.

Keywords Vesicoureteral reflux · Antibiotic prophylaxis · Urinary tract infection · Renal scarring · Pregnancy · Renal transplant

Introduction

Vesicoureteral reflux (VUR) is a common finding in pediatric patients. It has been noted to be present in one-third of patients evaluated after having urinary tract infections (UTIs) [1]. However, with improvements in prenatal imaging, a growing population of asymptomatic patients is also being identified as having VUR during post-natal evaluation for hydronephrosis. With the initial realization of this clinical entity and its association with renal injury and recurrent UTIs, a dogmatic approach of preventing UTIs—either by a surgical approach of correcting reflux, a pharmacologic approach of antibiotic prophylaxis, or therapeutic approach of optimizing bladder emptying—that would prevent long-term renal sequelae of VUR was generally accepted. However, over the past 20 years, there has been growing evidence that these previously held tenets to the treatment of VUR have not necessarily been "proven" to be consistently effective. This has led to subsequent questioning about almost all aspects of VUR—such as who should be evaluated, treated, and how to treat effectively—with sometimes conflicting recommendations from different parent organizations (American Academy of Pediatrics, American Urologic Association [AUA],…).

Background Studies of Vesicoureteral Reflux

The clinical significance of VUR as a pathologic condition came to medical attention over 60 years ago [2] with many of the original reports of significant disease morbidity and surgical approaches of treatment considered the standard of care. With improved imaging capability, it also became clear that VUR was fairly common among the general pediatric population experiencing UTIs, thus VUR was a fairly

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prevalent disorder but also one with potentially significant morbidity, presumably based off severity. In the late 1970s, with reports of successful VUR management with continuous antibiotics and not surgery [3], one of the first treatment controversies of VUR was sparked, while this disorder became one of interest to both pediatricians and urologists alike. However, early studies of VUR were often retrospective in nature, and of patients with more severe grades of, and risk of morbidity from, VUR, and subsequently were conducted without comparison to no treatment. Therefore, with the advent of evidence-based approaches to medicine in the 1990s, there was a noted gap in "quality" studies of VUR in children and admitted difficulty making evidence-backed recommendations in regard to its approach.

Several smaller studies in the early 2000s showed questionable benefit (no reduction in UTI frequency, increased antibiotic resistance) of the use of prophylactic antibiotics in the general pediatric population with VUR, again questioning another bedrock principle of VUR treatment. These controversial earlier findings prompted three larger scale, prospective studies somewhat concomitantly on three different continents. The PRIVENT study [4], Swedish reflux trial in children [5], and RIVUR study [6] all showed a reduction of symptomatic UTIs with the use of antibiotic prophylaxis, albeit limited only to females in the Swedish trial. Despite these larger prospective studies showing the benefit of prophylactic antibiotics in prevention of UTIs, there remain studies with conflicting results. Most recently, Hari et al. reported their prospective findings with antibiotic prophylaxis in 93 Indian children with VUR grades 1–4 [7]. They reported an actual increased risk of developing UTI, as opposed to simply no difference, with the use of antibiotic prophylaxis compared to placebo, in stark contrast to many of these recent studies. These findings, when combined in a meta-analysis with previous trials, result in skewing of the Forest plot data to show no difference between the use of prophylactic antibiotics compared to placebo in both dilated and non-dilated VUR [8].

However, a more critical examination of these studies and their populations reveals differences to potentially explain some of the contrasting results between trials. The subjects studied by Hari et al. were predominantly male (67%) with higher grades (3 or 4) of VUR (73%) [7], a population more similar to the Swedish reflux trial in terms of reflux severity, which showed a reduction of UTIs in females only. This is in definite contrast to the RIVUR study whose population was overwhelmingly female (91%) and with lower grades of VUR (> 75%) [6]. This argument regarding differing study populations is not unique and has been utilized both for and against validity of different results. However, trying to deduce general recommendations regarding approaches to a diverse disorder like VUR from studies of a heterogenous population may be a folly. Risk stratification of patients with VUR based off prenatal findings, presence of bowel bladder (or lower urinary tract) dysfunction, and recurrence of UTIs have been suggested by both US and European guidelines [8, 9], while consideration of age and possibly gender has also been suggested [10]. Approaches to each patient need to be individualized to their circumstances, even though there may be a dearth of statistical proof for every specific scenario.

Long-Term Risks of Vesicoureteral Reflux

The recommended goals in the treatment of patients with VUR has been the "preservation of kidney function by minimizing the risk of pyelonephritis" [9] or similarly worded "goals of… prevent recurring febrile UTIs (to) prevent renal injury" [8]. Historically, there has been a clear association between renal scarring, VUR, and the occurrence of UTI, which led to the conclusion that prevention of UTI or resolution of VUR will reduce renal scarring. However, there has been increasing anecdotal experience that new renal scarring occurs in the absence of documented UTIs and after the resolution of VUR, questioning this long-held notion. Renal scarring has been used as a surrogate for renal function, partially because it is a visual depiction of injury but also because it may occur earlier and presage the development of other signs of renal deterioration, such as proteinuria, hypertension, or decreased glomerular filtration rate (GFR). Pediatric patients with renal scarring have prevalence rates of hypertension ranging from 17 to 30% [1], far higher than the general pediatric population, while early proteinuria changes have been noted in slightly more than half of children with renal scarring [1].

In addition to the prevention of UTI, the RIVUR study also investigated the development of renal scarring as a secondary outcome. In their own secondary analysis of data, they found renal scarring associated with older patients (26 vs. 11 months), ultrasound abnormalities (hydronephrosis, duplication), higher grade of VUR, and the development of a second UTI before enrollment [11••]. A retrospective analysis of Taiwanese patients with primary VUR by Chen et al. looked at risk factors for both renal scarring and deterioration of renal function [12]. While they found that bilateral and higher grades of VUR were associated with both renal scarring and decreased GFR, an older age at diagnosis was associated with renal scarring, while younger age at diagnosis (along with scarring) was associated with GFR deterioration in multivariate analysis. Similarly, Matsuoka et al. examined those factors associated with worsening GFR in 51 subjects who had surgical correction of primary VUR performed 10 years previously [13•]. Similar to the study by Chen et al., bilateral and higher grades of VUR along with degree of scarring could almost exclusively predict those with decreased GFR. However, they also noted that older age at diagnosis, diagnosis without ever having a UTI, and proteinuria were associated with worse renal function postoperatively. Both of these studies noted significantly high percentage of patients with

hypertension, in addition to renal scarring, so it seems that renal scarring is an appropriate proxy for risk of renal deterioration.

One of the perplexities of the RIVUR study was the fact that there was no reduction in new renal scarring with the use of antibiotic prophylaxis, even though the use of antibiotic prophylaxis reduced the rate of recurrent UTIs and new renal scarring was associated with recurrent UTIs. This quandary of logic, or statistics, was addressed by a secondary analysis of the RIVUR study population by Wang et al. [14••]. Using propensity scoring within the model of their multivariate analysis, they were able to show that recurrent UTI-associated scarring was statistically more significant in those receiving placebo than antibiotic prophylaxis when adjusting for other factors, including baseline grade of VUR. Therefore, antibiotic prophylaxis was effective in prevention of both recurrent UTIs and associated renal scarring. However, the authors easily pointed out one of the conundrums with the RIVUR study data—there were equal number of patients with recurrent UTIs and new renal scarring as those with new scarring but no new UTIs during the study period—a finding that has been noted in preceding studies of VUR. Thus, the prevention of UTI may only be one factor in prevention of renal scarring.

The development of renal scarring in the absence of documented UTI has been seen prospectively in patients receiving follow-up imaging and is frequently detected in infants receiving baseline imaging. Unfounded scarring, especially when seen more diffusely, supports those proponents of the ureteral bud theory regarding the development of congenital anomalies of the kidney and urinary tract (CAKUT) that abnormalities in both the kidney and the ureter are derived from a single common mechanism which is programmed at an early stage of development [15]. In fact, the RIVUR study investigators, with such a large number of dimercaptosuccinic acid (DMSA) scan results to review, noted a significantly decreasing trend in mean DMSA uptake in non-scarred kidneys with VUR compared to those without and suggested that there may be "subtle intrinsic parenchymal changes" present in VUR that is not explained by infection [11••], potentially explaining new scarring that develops in VUR in the absence of infection. This precept would support the argument of different risk stratification for treatment, as those found to have VUR during the evaluation of prenatal hydronephrosis may have a different treatment focus than simply prevention of UTIs.

Several long-term studies from the mid-to-late 2000s examined predictors of chronic kidney disease (CKD) progression in patients with VUR. These factors have included bilateral renal scarring, presence of hypertension, and moderate proteinuria (urine protein-creatinine > 1) [16], with the latter two also predictive of disease severity in acquired glomerular disorders, like focal sclerosis and glomerulonephritis. Additionally, there is now clear evidence that the treatment of proteinuria and hypertension with renin-angiotensin system inhibitors can limit the progression of CKD [17], including congenital etiologies of disease, so treatment focus for some patients with VUR should include earlier identification of these treatable comorbidities.

Higher Grades of VUR

Clearly, distinctions should be made for higher grades of VUR, as there is greater risk in this population. This is often acknowledged by the fact that the highest grades of VUR were either excluded from, or limited in number in, these larger multicenter studies. Despite limited inclusion in some studies, higher VUR grade consistently associated with greater risk of morbidity. Additionally, children with dilating VUR (grades 3 and higher) may represent 12–16% of those presenting with UTI and up to 30% of newborns with prenatally detected hydronephrosis [18]. Therefore, this subset of VUR patients should be examined separately.

One of the largest, more recent studies of high-grade (4–5) VUR was a retrospective review of DMSA scans in Irish children over 15 years conducted by Hunziker et al. [19]. They found abnormalities in 38% of their 764 subjects, with age greater than 1 year, grade V VUR, and preliminary bowel and bladder dysfunction as significant predictors of scarring in this group. The authors highlighted the treatment of bowel and bladder dysfunction as one potential means of preventing scarring in this group. They separately noted that scarring discovered at less than 1 year of age was seen in a significantly greater proportion of boys, but admittedly prenatal hydronephrosis was the indication for VUR evaluation in < 1% of all subjects, questioning whether renal scarring may have been present, but not sought, in many older male patients. Subsequently, Nordenstrom et al. reported outcomes from their prospective randomized controlled trial of 77 infants with grade 4 or 5 VUR [20••]. Their population was predominantly male (71%) and identified with having VUR after a febrile UTI (also 71%) versus prenatal hydronephrosis (27%). Although their primary intent was comparison of early endoscopic treatment of VUR to antibiotic prophylaxis, they found no difference between treatment approaches in terms of UTI recurrence or renal deterioration on DMSA scan. However, they found that female gender and high post-void residual volumes at baseline were predictive of febrile UTI, and febrile UTI increased the probability of renal deterioration on follow-up DMSA scan, though no single variable predicted renal deterioration. The authors felt that this finding of high post-void residual volume at baseline, as well as high residual volumes and bladder capacities seen in follow-up, in those with renal deterioration underscored the importance of bladder function assessment in this infant population.

Martin et al. also reported the outcomes in 80 younger infants (less than 6 months of age) with dilated primary VUR over a 7-year period [18]. Prenatal hydronephrosis without UTI was the presenting finding in 43% of subjects, while

the remainder all had a single, confirmed febrile UTI leading to their initial VCUG. DMSA scan was obtained in all subjects before any subsequent UTIs developed; all received antibiotic prophylaxis, while surgery was considered if patients had a break through UTI, worsening VUR, or new scarring on follow-up imaging. They found that 64% of all subjects had improvement or resolution of their high-grade VUR. Predictors of improvement included a normal baseline DMSA scan (90% vs. 39%), remaining UTI-free during follow-up (77% vs. 39%), and not having grade 5 VUR. With only 25% of subjects undergoing surgery, a majority of patients had improvement without surgical intervention, prompting the authors to note that an initial non-operative treatment algorithm can result in natural improvement of high-grade VUR, especially in those with a normal baseline DMSA scan. These last two recent studies both showed no benefit from surgical intervention, even in the youngest patients with higher grades of VUR, highlighting that a conservative but vigilant approach in these patients may be warranted.

VUR During Pregnancy

The concern regarding VUR in pregnancy was based upon an early noted association between bacteriuria and adverse outcomes in pregnancy (pre-eclampsia, pre-term delivery, even fetal loss) from almost 55 years ago [21], while it was also noted that there was an increased incidence of VUR in pregnancy, secondary to other changes seen with the gravid pelvis [22]. Thus, bacteriuria was considered more likely to result in pyelonephritis during pregnancy and these added complications. With this presumption of risk, along with the fact that ureteral reimplantation becomes more technically difficult as females approach puberty with widening and deepening of the pelvis and enlargement of the venous plexus across the bladder surface, it was "long-held dogma…that unresolved VUR should be treated before a child progresses through puberty" [23]. In fact, the original AUA guidelines on VUR from 1997 [24] did not give specific recommendations for this population, but did "briefly address" the issue, giving credence to the sentiment that pyelonephritis risk may result in increased morbidity during pregnancy, especially for those women already with reflux nephropathy and reduced renal function. However, the expert panel did make two distinctions even then, that there may be a particular significance of pre-existing scarring in this population and there were very few studies on the outcomes of women with surgically treated VUR at that time.

This latter distinction was likely made in response to a 1995 study by Mansfield et al. which examined the pregnancies of 67 women with VUR during childhood [25]. They compared those who had the accepted approach of surgical correction of VUR when younger to those without correction, with both groups having similar mean VUR grade and rates of UTI recurrence during childhood. After 25 years, those with surgical correction of their VUR had 2.5 times higher rate of UTI during pregnancy (40%) compared to those uncorrected (14.6%). Although accounting for VUR grade and UTI recurrence rates when younger, the authors still attributed this difference to host factors. With this study and others having findings challenging the benefits of surgical correction of VUR in pre-pubertal girls, Hollowell reviewed the relevant studies on the topic in 2008, with the intent "to consider whether the perceived risks of reflux-related morbidity during pregnancy…constitute a valid indication for surgical intervention in girls with low-grade VUR" [26]. Reviewing 15 pertinent studies, she found the incidence of UTI during pregnancy was significantly higher in those patients with history of VUR and renal scarring (42%) compared to those with VUR and no scarring (22%). Interestingly, those diagnosed with VUR because of asymptomatic bacteriuria in childhood had a greater incidence of UTI in pregnancy (42%) compared to those diagnosed after symptomatic UTI (27%). Additionally, the pooled incidence of UTI during pregnancy was again higher in those who had undergone corrective surgery of VUR (44%) compared to those without surgical correction (20%), inclusive of the data from Mansfield et al.

Hollowell further analyzed the role of renal scarring on pregnancy outcomes, after noting one study which showed no episodes of pyelonephritis in women with VUR but no scarring (0%) while episodes occurred in those with VUR and scarring (3%) and those with no VUR but scarring (5%) [27]. She found that renal scarring in women with preceding VUR was associated with hypertension during pregnancy (31–42%), pre-eclampsia (10–14%), in addition to the higher incidence of UTI when compared to those without scarring. This led to the declaration of renal scarring as the "principal factor associated with morbidity during pregnancy" in women with history of VUR and the suggestion that conservative management of VUR, particularly in the absence of scarring, is unlikely to result in a greater risk of complications in pregnancy.

In the last 10-plus years since Hollowell published her findings, there have been few new studies on pregnancy outcomes of women with preceding VUR, not surprising given the two-plus decade gap between intervention and assessment of outcomes in this particular population. However, Roihuvo-Leskinen et al. did recently report pregnancy data on an original cohort of 213 Finnish girls diagnosed with primary VUR almost 40 years prior [28]. Originating as a study on girls with VUR and their voiding patterns as adults, the authors did not find that abnormal voiding patterns in adulthood was associated with greater risk of pregnancy complications, which was their original premise. However, they did note a high rate of renal scarring of 55% using ultrasound (not DMSA scans) in their adult cohort. Women with renal scarring had statistically higher rates of hypertension (33%), proteinuria (40%), and UTI (42%) during pregnancy than those without. While

proteinuria was also associated with hypertension (44%) and UTI during pregnancy (55%) compared to those without, fetal complications were not increased in either those with renal scarring or proteinuria. This study is notable for its rather high rates of renal scarring, especially given that scarring was determined by ultrasound, while it reiterates the greater risk of certain pregnancy morbidities, but not fetal complications, seen in women with VUR and renal scarring or proteinuria.

Kidney Transplant Recipients

With such a large percentage of pediatric patients developing end-stage renal disease secondary to CAKUT, appropriate evaluation of the lower urinary tract has long been recommended for pediatric renal transplant recipients. The primary focus in this evaluation has typically been the functionality of the bladder, to avoid issues of hydronephrosis to the renal graft, urosepsis in the setting of immunosuppression, or other preventable morbidities. Guidelines from Europe have understandably recommended nephroureterectomy in pediatric transplant recipients with chronic UTI, severe renovascular hypertension, risk for renal cancer, and heavy proteinuria, but separately included those with "massive" VUR [29]. Presumably, this recommendation was made because of the future infection risk inherent in high-grade reflux, though commentary on the guideline specifically cite that this recommendation to be considered "independent of infection" [29]. However, in the absence of recurrent UTIs, especially with the growing number of patients with high-grade VUR without documented infections, this recommendation would seem less stringent. In a review of nearly 20 years of native nephrectomies in pediatric transplant recipients, Sharbaf et al. found limited benefit of nephrectomy in the prevention of UTI recurrence [30]. Although a majority of their 49 patients had nephrectomies performed for other purposes, nine had nephrectomies performed to limit UTI recurrence. Two-thirds of these nephrectomized patients still had at least one UTI, with a median of three UTIs, within 2 years of transplant. There was no formal VUR evaluation performed in these patients, as the study's primary focus was not on UTI prevention, but those with post-transplant UTI recurrence all had other lower urinary tract risk factors for UTI, such as incomplete bladder emptying; however, the removal of the native kidney and ureter did not address the issue of UTI recurrence.

Similar to native VUR, there has been recent increased interest, and equal consternation, as to the best approach to ameliorate VUR morbidities in the transplanted kidney. There is greater concern about VUR in this population because not only is the graft a solitary functioning kidney, but there is presumed greater susceptibility to infection with immunosuppression. The significant prevalence of VUR in adult kidney transplant recipients has been promulgated as an "important cause of (late) graft failure" for over 40 years [31]. Similarly, high VUR prevalence rates were also reported in pediatric renal transplant recipients almost 30 years ago [32] with high rates of transplant pyelonephritis seen [33], leading to similar discussions within the pediatric transplant community about best practices to minimize VUR development in the graft and optimal mitigation strategies when symptomatic VUR occurs.

Two European studies from the early 2000s showed a clear association between acute pyelonephritis episodes in pediatric patients with transplant VUR. Ranchin et al. noted a high prevalence of transplant VUR (60%) and ureteral dilation (32%) when VCUG was performed standardly post-transplant in 55 pediatric recipients [34]. After excluding UTI episodes that occurred with a catheter present, there was a higher proportion of pyelonephritis episodes seen in those with VUR compared to those without. Similarly, Couthard et al. reported a high rate of transplant VUR (70%) seen in their 30 patients [35]. Performing DMSA scans within 2 weeks of transplant function and 1-year post-transplant, a very high rate of new renal scarring (37%) was seen on follow-up scans, with multiple new defects seen in 17% of subjects. New scarring was not associated with VUR alone but was associated with the occurrence of any UTI, and more so if UTI occurred with transplant VUR. Not surprising, those with multiple areas of new scarring were found to have lower mean graft function than those with no or a single area of new scar. Unfortunately, the prolonged presence of ureteral stents, 3–6 months in this particular study, affected the rates of pyelonephritis and renal scarring seen, but these studies showed that the greatest risk seen with transplant VUR is likely the risk from pyelonephritis and renal scarring.

There has been subsequent focus on who may be at greater risk of developing transplant VUR and whether certain preemptive measures could reduce its incidence. An adult study by Molenaar et al. performed a VCUG standardly 1 week post-transplant in just over 1000 kidney transplant recipients [36•]. Their incidence of transplant VUR was only 10.5%, lower than reported in most pediatric studies, because of the small percentage of adult recipients with primary urologic pathologies. Nevertheless, in this large study, there was no difference in the rate of VUR based off stenting technique used (double-J vs. external stent vs. none), but there was higher VUR and UTI incidence with extravesical (vs. intravesical) ureteral reimplantation. Studies in pediatric recipients, more limited in sheer numbers, have not yet shown significant differences in VUR rates between surgical approaches, but may be unable to achieve statistical significance for any differences. The high rates of renal scarring noted by Couthard et al. mentioned previously [35] conferred that prolonged stent presence did not affect the rate of transplant VUR but did increase the risk of renal scarring.

In a recent pediatric transplant study, Routh et al. reviewed their risk of urologic complications including transplant VUR [37], standardly performing a VCUG at 3 months post-

transplant. One-third of their subjects had an associated urologic pathology, with posterior urethral valves (PUV) and reflux nephropathy being the most prevalent at 13 and 8%, respectively. They noted transplant VUR in only 10% of their 211 procedures and found those with transplant VUR were more likely to have a primary urologic pathology (37% vs. 4%, $p = 0.002$), but this difference was driven primarily by patients with PUV. In multivariate analysis, transplant VUR was only associated with having PUV—not age, gender, or other urologic pathologies. Similarly, a multicenter study of febrile UTIs after kidney transplant found that those with PUV had significantly more frequent post-transplant UTIs than those without ($p = 0.004$), though rates of transplant VUR were not reported [38]. This study also noted that patients with a history of febrile UTI prior to transplant had a higher rate of febrile UTI post-transplant than those with no prior history. The identification that patients with PUV are at greater risk of developing certain post-transplant complications is consistent with recent long-term outcome data. McKay et al. reviewed 30 years of transplant registry data from Australia and New Zealand [39•], comparing outcomes in children with renal dysplasia, reflux nephropathy, and PUV, and found that patients with PUV had significantly lower 20-year graft survival rates compared to those other two congenital etiologies, after adjusting for age, graft source, and antigen matching. They speculated that the bladder dysfunction seen in PUV may be the source of this increased risk. Conversely, Torricelli et al. reported no differences in graft outcomes based off of ESRD etiology [40], with 31% of their 305 pediatric recipients having a primary urologic disorder. However, they strongly advocated aggressive pre-transplant evaluation and intervention with intermittent catheterization in all patients with difficulty spontaneously draining their bladder, attributing their low rates of symptomatic VUR (3.6%) to this preoperative regimen. Therefore, it would seem that identification of higher risk populations, such as boys with PUV or those with prior history of febrile UTI pre-transplant, is justifiable with more conservative management pre-transplant or greater vigilance post-transplant being warranted.

Following transplant, if symptomatic VUR is present, it is still unclear as to the optimal approach to prevent morbidity. Most recent studies have reported initially using prophylactic antibiotics in subjects identified as having post-transplant VUR [34, 40, 41], but also note a significant portion of subjects needing surgical intervention for recurrence of UTIs. The previously mentioned study by Weigel et al. reported limited effectiveness of antibiotic prophylaxis in the prevention of febrile UTIs post-transplant, as it was utilized in most of their children who experienced a febrile UTI [38]; however, they did not assess for post-transplant VUR. They found that almost half of all febrile UTIs occurred in the first 6 months post-transplant, though occurred significantly later in girls than boys, so presumably may have occurred in girls because of conditions other than VUR. In those patients receiving surgical intervention for transplant VUR, there are quite different results than seen in primary VUR. Torricelli et al. reported great success with endoscopic polymer injections to treat transplant VUR, with no complications and only one patient having recurrent UTIs following intervention [40]. However, more recent reports on the effectiveness of endoscopic injection for transplant VUR in children have not been as promising. Sheth et al. described their outcomes with post-transplant VUR, with surgery reserved for those with febrile UTIs or worsening hydronephrosis and elevated creatinine levels [42•]. In their 11 subjects who had endoscopic injection, they noted failure of the initial procedure in all patients and a subset of patients getting repeat injections having a 50% complication rate. Conversely, their 7 subjects who had a redone ureteral reimplant needed no further interventions with only a single non-febrile UTI developing while the ureteral stent was in place. Similarly, Wu et al. noted very limited success with endoscopic injection in their pediatric transplant recipients, while excluding more complicated patients with PUV or neurogenic bladder [41]. They noted VUR resolution in only 22% of those treated endoscopically, lower than the reported cumulative success rate of 50%, while also reporting significant difficulty with revised reimplantations following an initial endoscopic treatment. Not surprisingly, both groups endorsed open ureteral reimplantation if surgical intervention of transplant VUR was needed.

The concept that transplant VUR implicates more risk than just infections has also been raised. Chu et al. analyzed their pediatric renal transplant recipients with graft hydronephrosis, present in 49% of their recipients [43]. Unfortunately, VCUG was not standardly performed to determine the overall prevalence of VUR, though their hydronephrosis cohort had a high incidence at 71%. This same cohort had a significantly higher incidence of pyelonephritis, lower estimated GFR in follow-up, but also higher rate of acute rejection than those without hydronephrosis. Additionally, the GFR in those with hydronephrosis and rejection was significantly lower than those without hydronephrosis but with rejection, accounting for the differences in GFR seen between those with and without hydronephrosis. The authors speculated that not all of the treatment focus in transplant hydronephrosis should be on the obstruction relief or prevention of infection, but should also raise the suspicion of rejection. Recently, Wu et al. assessed differing treatment approaches based off the patient's initial presentation with transplant VUR [41]. Excluding patients with known bladder issues, they analyzed patients who were symptomatic with either recurrent febrile UTI or graft hydronephrosis, while discovering a third asymptomatic group of transplant VUR patients, those found only with abnormal inflammatory changes consistent with VUR on screening biopsy. This latter group was treated similarly to those with graft hydronephrosis, with improved bladder

emptying and antibiotic prophylaxis, and spontaneous resolution of transplant VUR occurred over time. The authors noted that this less aggressive, non-surgical approach is similar to that advocated in infants with prenatal hydronephrosis and high-grade VUR. However, the similarities between the VUR in those with prenatal hydronephrosis and those with incidental transplant biopsy findings may not end just there, as perhaps these populations share a similar mechanism of injury of non-infectious renal scarring.

Conclusions

Similar to primary VUR, there have been many recent challenges to the previously held tenets of care for VUR in specialized populations as well. A singular approach to this more nuanced disorder can no longer be utilized and treatment approaches must be individualized to each particular patient. Like in primary VUR, the recurrence of febrile UTIs is a likely predictor of future sequelae in those with higher grades of VUR, pregnant women, and even those with renal transplant. So, in those deemed at risk for recurrent UTIs, the prevention of UTI either surgically or non-surgically is a valid pursuit. However, those seemingly not at increased risk of UTI recurrence, treatment focus may center more on addressing bladder dysfunction and the early identification of renal scarring. While renal scarring portends certain risk, it may occur in the absence of infection both in primary low-grade VUR as well as these other specialized populations. Its presence should prompt aggressive screening and treatment of findings such as proteinuria, hypertension, and possibly even transplant rejection.

Compliance with Ethical Standards

Conflict of Interest The author declares that he has no conflict of interest.

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- •• Of major importance

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