

## Platinum Priority – Editorial

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# Modern Management of Vesicoureteral Reflux: Envisioning a Future with Individualized Therapies

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Management of vesicoureteral reflux (VUR) remains controversial. The recently updated European Association of Urology/European Society of Paediatric Urology guidelines described by Gnech et al [1] summarize the current literature and provide a roadmap for clinicians caring for children affected by reflux.

The main goal of VUR care is prevention of recurrent febrile urinary tract infections (UTIs) and renal injury, yet we still lack answers to several key aspects of care. Renal damage is caused by either renal dysplasia secondary to interference with renal development in utero, or recurrent pyelonephritis in some but not all children. This suggests that only a subset of reflux patients may benefit from active treatment, which has led to attempts to reduce the diagnosis of clinically insignificant disease.

The first controversial aspect regards screening. Reflux is diagnosed either during workup for perinatal hydronephrosis or after a UTI. Not all newborn infants with prenatal hydronephrosis confirmed to be persistent after birth need testing for VUR. Selective testing will prevent overdiagnosis of lower grades of VUR with a lesser clinical impact. Children with indirect evidence of VUR such as ureteral dilation or parenchymal scarring or other congenital abnormalities of the urinary tract should instead be screened. It is in these patients that reflux is of greater clinical significance.

Following a febrile UTI, the most useful evaluation remains uncertain. Renal and bladder ultrasound can screen for the effects of VUR as well as other congenital renal anomalies. However, it has become clear that this is not an effective tool in screening for VUR, even for higher grades [2]. More specific evaluation may be performed using the

“bottom up” approach of performing a cystogram to definitively identify or rule out VUR. Conventional radiography and the more recent contrast-enhanced voiding urosonography [3] are very effective tools.

Concerns regarding a voiding cystourethrogram (VCUG) include the invasiveness of catheterization, radiation exposure, and identification of clinically insignificant VUR, which could lead to overtreatment. A “top down” approach involving an acute dimercaptosuccinic acid (DMSA) scan in UTI cases to identify renal injury identifies the children most likely to have clinically significant VUR. This reduces the number of VCUG procedures but is associated with higher costs and radiation exposure [4] and children are at higher risk of recurrent febrile UTI [5].

Another contentious issue is the use of continuous antibiotics prophylaxis (CAP) to reduce UTIs and pyelonephritis. While use of antibiotics for lower-grade reflux can be avoided, the consensus is that children with high-grade reflux benefit the most. This has been demonstrated in the Swedish Reflux Study [6] and two large randomized multi-institutional clinical trials, RIVUR [7] and PREDICT [8]. The RIVUR trial demonstrated a 50% reduction in UTIs with CAP, but failed to show a significant reduction in renal scars. However, the study was not powered for this outcome, making it difficult to draw any firm conclusions regarding the impact of CAP on scarring. The recent PREDICT trial also showed a similar reduction in UTIs. Both studies reported a significant increase in antibiotic resistance among patients in the treatment arms, although the clinical impact of this is unclear. The PREDICT trial confirmed that ~30% of patients with VUR had signs of

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nephropathy before the development of any infection, and that the development of new scars was not closely associated with UTIs. A similar rate of new defects on DMSA scans (19%) was found whether or not children developed a UTI. Thus, not all patients benefit from CAP, and the decision to initiate CAP should ideally be made after discussing the risks and benefits with the family. Furthermore, we are still missing a key factor in determining who is at higher risk of developing renal damage. Not all children with VUR and infections will develop scars, indicating that host-related immune responses and bacterial virulence play a major role in the pathogenesis of renal damage. Future research should focus on serum or urine biomarkers that can identify patients susceptible to scar formation after pyelonephritis.

Another controversial topic is the decision to intervene surgically. While most would agree that patients with recurrent breakthrough infections while on CAP are appropriate surgical candidates, there is no consensus on the management of persistent high-grade VUR in older patients. It can be argued that if an older child has been infection-free off CAP, they are at low risk of complications. However, several situations might warrant surgical correction despite a lack of pyelonephritis, such as older girls with reflux, for whom the goal is to avoid the risk of pyelonephritis in pregnancy, or patients with high-grade reflux, which could lead to incomplete bladder emptying and potentially bladder dysfunction.

Finally, the current guidelines on VUR briefly touch on bladder-bowel dysfunction. Screening and aggressive management of voiding dysfunction and constipation should be the cornerstone of therapeutic strategies for all potty-trained children with VUR, as these conditions not only increase the risk of infection but also hinder spontaneous VUR resolution.

Much remains to be both learned and decided on in relation to VUR. More specific predictors of the risk of infection and renal injury are needed to tailor evaluation and therapy for those who need it most. In the future, clinical factors such as age, gender, prior infections, degree of reflux, presence of other congenital renal anomalies, and bladder-bowel dysfunction will be integrated with

biological data, such as host immune response factors and microbiome analysis for individualized risk assessment. It is essential to develop safety thresholds for children with UTIs and VUR to offer families and providers guidance in terms of choosing the most appropriate management options for their level of risk tolerance and therapeutic preferences. In the meantime, physicians should continue to offer shared decision-making to families after a thorough discussion of the pros and cons of each diagnostic and therapeutic approach.

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