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Review

Vesicoureteral reflux: A historical perspective

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Abstract
The management of vesicoureteral reflux is a mainstay of pediatric urology. This management however, has evolved considerably throughout the years due to a dynamic understanding of both pathology and the relationship between surgical and medical therapies. The purpose of this article is to provide the reader with a historical perspective on management and delineate how its past has shaped current therapies and guidelines.

Introduction

If there was a specialty defined by an anomaly it would have to be that of pediatric urology and vesicoureteral reflux (VUR). With a recent meta-analysis demonstrating a prevalence of up to 9% in children [1], it is easy to imagine that in a typical day in the office of a pediatric urologist a significant amount of time is spent managing reflux. That management, however, has evolved considerably throughout the years based on changing concepts of VUR and its inherent risks. One needs only to consider the changes in our perception of VUR since its clinical significance has been realized to appreciate this evolution. The innovations of surgical technique and technological advances have been balanced by the use of antibiotic prophylaxis and non-surgical management. The purpose of this article is to provide the reader with a historical perspective on management and delineate how its past has shaped current therapies and guidelines.

On receipt of the American Academy of Pediatrics Medal in Urology in 2003, Barry O'Donnell listed the following concepts which had been mainstays of VUR management and have since become fallacies:

1. Vesicoureteral reflux is rare.
2. Vesicoureteral reflux is progressive.

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3. Grading of reflux is not important.
4. Bladder outlet obstruction causes vesicoureteral reflux.
5. Vesicoureteral reflux is always bilateral—eventually.
6. Vesicoureteral reflux always causes progressive renal disease.

In the beginning

The discovery of ureteral anatomy and the function of the ureterovesical junction can be seen in the early experiments of Galen, the drawings and discussions of Leonardo da Vinci, and the dissections of John Sampson. Da Vinci postulated an anti-reflux mechanism to prevent urine from returning into the upper tracts [2]. John Sampson determined that it was the detrusor backing of the ureter that allowed for one-way urine flow [3]. It was not until the 1950s, however, that Hodson and Edwards discovered the association of VUR with renal scarring from bacterial infection [4]. This discovery was backed by an abundance of research demonstrating an exponential relationship between number of urinary tract infections, the grade of reflux and renal scarring. Working within this concept, there was concern that uncontrolled reflux would eventually lead to reflux nephropathy and end-stage renal disease.

In 1952, Hutch performed the first antireflux surgery in paraplegic patients. Dedicated to the investigation of the relationship between VUR and upper tract damage, his procedure paved the way for other reimplantation techniques [5]. In 1958, Politano and Leadbetter introduced a new surgical corrective procedure for VUR: intravesical ureteral reimplantation. Compared to prior surgical therapies which aimed to reduce resistance at the bladder neck, ureteral reimplantation negated the concept that bladder outlet resistance was the major cause of reflux [6]. While variations in the Leadbetter–Politano reimplantation have been developed, its basic mechanism of surgical correction remains. As a reliable and reproducible procedure when performed by an experienced surgeon, ureteral reimplantation became the gold standard therapy for treatment of VUR. We were now given the opportunity to diagnosis and easily correct a condition which threatened the functionality of the kidney. Healthy children with reflux underwent surgical correction and ureteral reimplantation was a principal tool in the repertoire of the pediatric urologist.

Changing gears

Ureteral reimplantation was hailed as paramount in the management of VUR for nearly 20 years until the work of Edwards et al. [7]. In 1977, they reported high rates of spontaneous resolution of reflux (71%) on low dose continuous antibiotic prophylaxis (CAP). It was noted that more severe reflux was less likely to resolve, but their work also highlighted that while on CAP, there was a decreased chance of developing new renal scars [7]. The idea of surveillance on CAP was also supported by the work of O'Donnell et al. [8] and Lenaghan [9]. These groups demonstrated that children with VUR on continuous antibiotics had less renal damage than those who received episodic treatment for urinary tract infections. Continuous antibiotic prophylaxis for "refluxers" became customary, with maintenance of therapy until resolution or surgical fixation.

Prolonged antibiotic prophylaxis in children soon became a topic of debate. The paucity of randomized controlled trials challenged the concept that even low grade reflux required continuous antibiotic prophylaxis until resolution. Early randomized controlled trials such as the International Reflux Study and the Birmingham Study compared children on antibiotic therapy with those that underwent surgical correction. A "non-treatment" arm was not part of the study design due to the notion that non-treatment placed the patient with reflux at significant risk and endangered patient safety. Clinical trials began to target the safety of stopping antibiotic prophylaxis in select patient populations to determine the development of UTI and/or renal scarring.

There have been 8 randomized controlled trials (RTC) comparing CAP to no prophylaxis in patients with VUR. Half of the trails determined that prophylaxis was not helpful (and in some cases harmful), while the other half demonstrated that continuous prophylaxis reduced the risk of symptomatic or febrile UTIs by up to 37%. With an even split, the decisions that pediatric urologists face when managing patients with VUR are complex and not always clear. Upon closer examination of these RTCs, it is evident that the study populations were quite different. In those 4/8 studies which indicated no benefit to continuous prophylaxis, the study populations were predominantly low grade refluxers, commonly but not exclusively, without consideration of bladder and bowel dysfunction. Although the option of foregoing antibiotic prophylaxis in patients with low risk reflux has clearly been demonstrated, further investigation into this area is indicated and careful discussion with parents about the options is crucial. One assumption that is often made in these studies is that low *grade* reflux is equivalent to low *risk* VUR and that high *grade* is equivalent to high *risk* VUR, which is a dangerous oversimplification.

Innovations

In addition to the management of vesicoureteral reflux, the timing of diagnosis has also evolved over the years. The 1980s brought about the routine use of prenatal imaging. Prior to this time, vesicoureteral reflux was primarily identified after the onset of a febrile urinary tract infection. Prenatal ultrasound recognized upper tract dilation with or without renal dysplasia in asymptomatic patients, leading to postnatal investigation and possible identification of VUR prior to development of a symptomatic UTI and acquired renal damage. In 1993 the Society for Fetal Urology (SFU) issued recommendations for postnatal investigation of antenatal hydronephrosis in order to identify and treat clinically significant pathology prior to development of symptoms. In order to standardize terminology and guidelines for postnatal investigation, Nguyen et al. proposed a multidisciplinary consensus on antenatal upper tract dilation [10].

Along with the use of prenatal ultrasound, the 1980s was also significant for the introduction of a standardized grading system by the International Reflux Study Committee. Voiding cystourethrogram (VCUG) allowed for demonstration of reflux on imaging studies. The guidelines provided by the SFU and further classified by Nguyen, et al. proposed imaging studies for patients who present with certain criteria. The International Reflux Study Committee delineated five grades of reflux based on the VCUG, and discussions of management became more specific. Reflux grading allowed separation into lower and higher grades, promoting investigation into varying therapy depending on the grade of reflux. That being said, assessing risk in vesicoureteral reflux using reflux grade alone offers a limited, and often skewed assessment of which children will continue to be symptomatic from reflux.

When discussing vesicoureteral reflux, one must be aware of its association with bowel and bladder dysfunction. Initial surgical treatment for VUR attempted correction of intravesical pressure by approaching the bladder neck. Following establishment of the Leadbetter–Politano reimplantation, focus transitioned more specifically to the ureterovesical junction. It was only later that we began to appreciate the complex relationship between bladder neck, bladder, and incompetent UVJ. The International Reflux Study's European branch identified a population of children with "bladder ureteral dysfunction", who had increased risk of urinary tract infections, persistent reflux, and variability in reflux grading between imaging studies [11]. Numerous reports have confirmed bladder bowel dysfunction as an independent predictor of low reflux resolution rates and increased breakthrough infections. With our evolving understanding of bladder bowel dysfunction being possibly both a radiologic, as well as a behavioral abnormality, approach to treatment has changed. Management of patients with bladder bowel dysfunction incorporates behavioral modification but also poses a unique challenge in predicting outcomes. The most recent AUA guidelines on VUR emphasize the importance of the management of bladder and bowel dysfunction in children with VUR. These recommendations aim to reduce the risk of upper tract infections and renal scarring, maximize spontaneous resolution, as well as increase success rates of corrective procedures [12]. It is clear that this interplay will become a key component in future discussions.

At the turn of the century, pediatric urologists followed suit in the general trend of surgery, attempting to incorporate minimally invasive surgical techniques. Although endoscopic injections for treatment of VUR was introduced in the 1980s, the procedure rapidly gained popularity in the United States when the FDA approved dextranomer/hyaluronic acid (Deflux) in 2001. Lendvay et al. investigated the evolving trends in the treatment of VUR with the availability of endoscopic therapy. Their study demonstrated a 143% increase in the number of VUR procedures per institution per year between 2001 and 2004 in children's hospitals in the United States [13]. These results were corroborated by Caleb and Copp et al. who showed that between 2002 and 2006 the treatment of reflux using early endoscopic intervention almost doubled, due to endoscopic correction [14]. This trend, however, has not been sustained and, in fact, a significant decrease in the use of endoscopic correction in the United States was seen from 2006 to 2011 [15]. Most pediatric urologists still struggle with the role of endoscopic correction: does it replace ureteral reimplantation, is it a substitute for antibiotic prophylaxis, or is it a temporizing measure to allow children to get through a period of time when they are susceptible to UTIs?

Future

With the development of endoscopic and minimally invasive surgical interventions, changes in antibiotic prophylaxis regimens, and the latest assessment of the safety and success of traditional ureteral reimplant, several sets of guidelines have been issued and updated. Management of VUR continues to be a dynamic subject, often with large variations in practice patterns between early intervention vs. observation only. The future is replete with potential for research. Future study is likely to further stratify VUR patients into those who are at high risk for renal damage versus those with low risk, and will allow us to better individualize and manage care.

Conflict of interest

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