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Review Article

Have we Overtreated Children with Vesicoureteric Reflux?

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ABSTRACT

Urinary tract infections (UTI) are the most common serious bacterial infections in young children. These UTIs have a high association with vesicoureteric reflux (VUR). The pathophysiology of VUR's renal sequelae, its investigation and management is presently undergoing a reassessment. This review documents these changes focusing on compelling new data. With regard to the need for and benefit of imaging procedures in children with UTIs we present an algorithm for investigation that is tailored to the African context. The value of continuous antibiotic prophylaxis is questioned and the role of injectable ureteric bulking is discussed with reference to the Swedish Reflux Trial.

Key Words: Vesicoureteric reflux, children, etiology, pathophysiology, investigation, managment

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INTRODUCTION

The traditional modes of investigation and management of primary vesicoureteric reflux (VUR) in children is undergoing a dramatic revision. VUR has been called the "prostate cancer" of Paediatric Urology, recognition that VUR has been over investigated and perhaps in many cases over treated.

This paper aims to define contemporary best practice for children with VUR based on the emerging available evidence. VUR's etiology, pathophysiology, presentation, investigation and management will be discussed.

Paquin (1959) first proposed that a short intramural ureteric tunnel accounted for "lateral ectopia" and this is what we define as primary VUR.[26] It is estimated that as many as 8% of girls and 2% of boys will have a urinary tract infection (UTI) by the age of 7 years[19]. A third of these UTIs are associated with VUR[17]. In our African context the incidence of VUR is suspected to be lower than this, as American data suggests that black children have a 10-fold lower VUR incidence than white children[27].

Traditional clinical approach: Two milestones have guided the traditional clinical approach to VUR. The first was a landmark study of VUR in a pig model by Phillip Ransley of Great Ormond Street Children's Hospital, London[24]. He demonstrated a simple equation that has stood the test of time. VUR when associated a UTI leads to chronic pyelonephritis with resultant renal scarring, hypertension and eventually end stage renal disease. This work provided the rationale for antibiotic prophylaxis since VUR in the absence of infection is a benign entity.

The International Reflux Study (IRS) represents the second milestone in our traditional understanding of VUR[1, 2] The IRS randomised children to either surgical reimplantation combined with antibiotic prophylaxis versus prophylaxis alone. The study showed no difference in the rate of recurrent UTI's or renal scarring, therefore adopting a policy of prophylaxis as first-line therapy for VUR. However, febrile UTI's (i.e. pyelonephritis) were lower in the surgery arm. This finding guided the practice that children who failed conservative treatment underwent surgery. The IRS thus represented a powerful stimulus to guide treatment of VUR and crucially provided a motivation for surgical intervention. Essentially, all children with VUR were placed on prophylactic antibiotics, and if this failed surgical correction was recommended.

The IRS's impact on clinical practice can be seen from our own unpublished data over a 15 year period (1992 – 2007). During this period 190 children were treated for VUR. Of these the majority had Grades I – III VUR. Roughly, 50% of the total cohort either underwent immediate surgery or initial conservative treatment followed by surgery. This represents a high number of children undergoing surgery for VUR, an approach that has been questioned in recent literature.

A major limitation of the IRS was that it never included a placebo or observational arm[21]. Thus the superiority of prophylaxis or surgery over surveillance was never actually established. Furthermore, the data from the IRS and similar studies have undergone meta-analysis and it is estimated that 15 children on prophylaxis need to be reimplanted to prevent 1 febrile UTI at 5 years follow-up[17].

To summarise, as Paediatric Urologists we have been basing many decades of VUR management on poorly controlled data, which had at best shown a marginal benefit for surgery.

Problems with the traditional management of VUR: Doubts regarding the traditional care of children with VUR began to surface with greater understanding about the natural history of VUR and the publication of 4 well designed clinical studies.

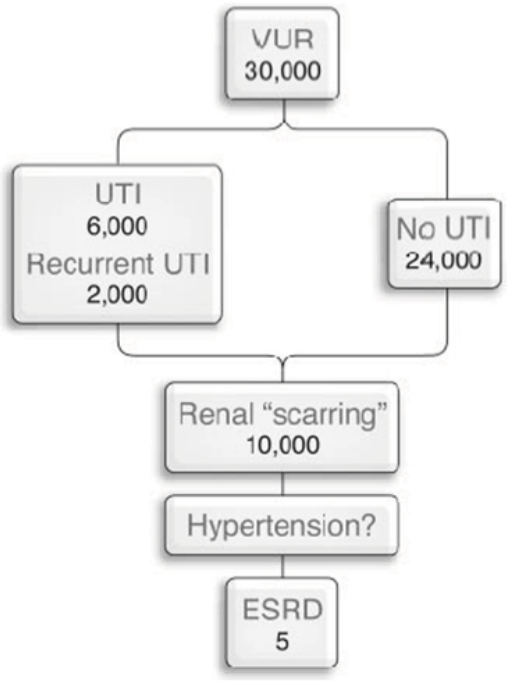

Fig. 1: Natural history of VUR, from a population of 1,000,000 children (assuming a prevalence of VUR of 3%)[5].

Ransley's work had provided compelling proof of the dangers of VUR, yet newer work has cast doubt on the extent of the association of VUR, UTIs and renal damage. It has been shown that "dilating" VUR (i.e. Grades III-V) have a six fold greater chance of producing renal scarring than Grades I-II[3]. Yet this seemingly obvious linear association is not always borne out. Renal scarring occurs in some children in the absence of VUR and yet does not occur in many cases of severe VUR[4]. Other factors must thus be at play since longitudinal studies suggest that renal damage exists even before the 1st UTI and that in fact few new abnormalities arise after a UTI[17]. This suggests that the pathophysiology of the renal parenchymal anomaly associated with VUR may in fact exist antenatally – the so-called reflux-congenital renal hypoplasia/ dysplasia syndrome[18]. Williams et al have postulated that rather than UTI or VUR, it is this parenchymal anomaly that is the key to the pathophysiology[17].

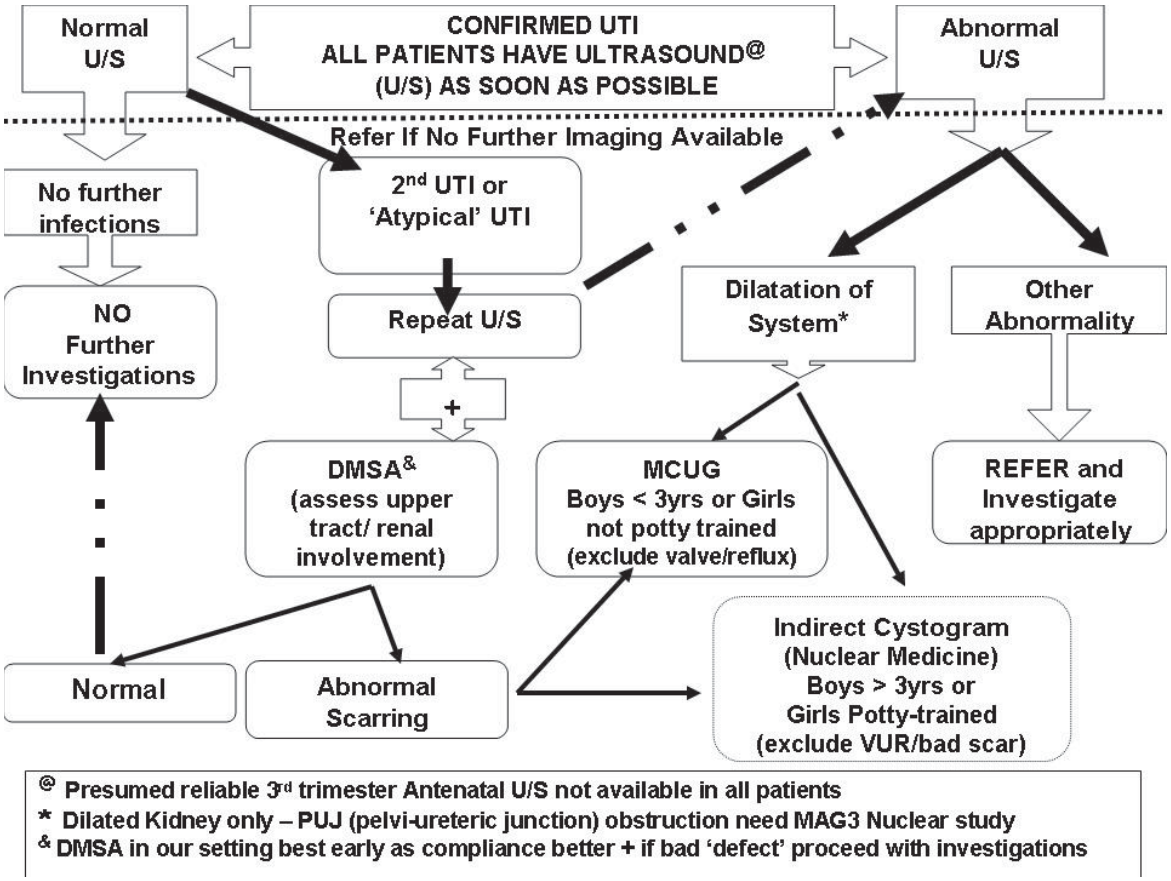

Fig. 2: Red Cross Children's Hospital UTI investigation protocol. The need to confirm a UTI prior to investigation is emphasised, a renal sonar in all patients, but reservation of further imaging for those with abnormal sonar or recurrent UTI[16].

Regarding the natural history of VUR, it is recognized that most cases spontaneously resolve by the age of 2 years. As is shown in Fig. 1, an assumed VUR prevalence of 3%, would yield an incidence of 30 000 children in a cohort of 1 million. Yet only 5 out of those million children would be expected to progress to end stage renal disease (ESRD)[5]. Malone has estimated that to prevent one case of ESRD, $5 million dollars will be s3pent to investigate otherwise healthy children[6].

To summarise, longitudinal VUR studies have cast doubt on the conventionally understood pathophysiology of VUR and hence the benefits of treatment. They point to VUR's natural history in that most cases resolve, 30% will have recurrent UTI, but few develop major renal sequelae[17].

Additional evidence of over treatment comes from four recent trials looking at the effect of antibiotic prophylaxis on UTI prevention. All studies surprisingly showed no reduction in UTIs with prophylaxis[7-10] These studies thus question the established first line role of antibiotic prophylaxis in the management of VUR.

This growing skepticism culminated in a Cochrane Collaboration review which made the startling conclusion that: "it is uncertain whether the treatment of children with VUR confers clinically important benefit[11].

Revised guidelines for VUR investigation: If the evidence to treat VUR is inadequate, we should ask if the link between VUR, UTIs and renal scarring is significant enough to warrant detection. The answer to this vexing question must lie in less invasive and more selective investigation protocols.

The United Kingdom's National Institute for Clinical Excellence (NICE) produced dramatically revised VUR guidelines in 2007. These make reference to the fact that

investigation of VUR in children is invasive, costly and often produces information of little clinical significance[12].

Standard VUR investigation protocols have for decades required an MCUG in addition to ultrasound. Despite its invasiveness, the MCUG remains the second commonest investigation requested by Paediatric Urologists. In one study, girls who have undergone ureteric reimplant for VUR recalled the MCUG more than the surgery[14]. Additionally, concerns exist about the cancer risk associated with X-ray exposure. An MCUG has an estimated cancer risk in children of 1:2500[15]. The deleterious effects of ionising radiation are well known. In children, especially, the goal is to use a dose that is "as low as reasonably achievable" (the ALARA principle)[13].

These traditional approaches to investigation place emphasis on the MCUG in what has been termed the "bottom up approach". Evidence has accumulated which supports rather a "top down approach". Here renal status via nuclear imaging is prioritised.

The Red Cross Children's Hospital in Cape Town, South Africa has recently adopted a new protocol (Fig. 2). The protocol's aims were two-fold. Firstly, it recognises evidence based changes in our understanding of VUR's significance. Secondly, we wished to produce a protocol appropriate to a developing-world medical environment.

The 2007 NICE guidelines for the investigation of UTIs have caused great controversy in the UK with its dramatic reduction in imaging requirements. NICE's protocol is more radical than the Red Cross Children's Hospital's guidelines in reducing imaging. With NICE guidelines patients over six months would not automatically get an ultrasound.

Malone et al sought to test the new NICE protocol with traditional practice. They found that 83% of renal sonars required by traditional protocols would be classified by the new NICE guidelines as inappropriate. "Anomalies" were detected in only 2.6%, but these were typically of little clinical significance[6]. These data serve to support the claim of over investigation by traditional protocols.

VUR management revised: Traditionally, VUR management required long-term antibiotic prophylaxis with open ureteric reimplantation reserved for failures of conservative treatment. This has undoubtedly resulted in over treatment of some children. This raises the critical question of how can we select the few children in whom VUR is significant so as to avoid over treating the majority?

Previously, mention was made of trials that called into question the value of antibiotic prophylaxis. A recent well conducted Australian study, the PRIVENT trial, supports an ongoing role for prophylaxis (Fig. 3). Craig el al,[19] randomized 600 children following their 1st UTI to either placebo or antibiotic prophylaxis. Their mean age was 14 months, 64% were girls and 42% had proven VUR. They demonstrated a statistically significant 6% reduction in the risk of febrile UTIs that was more pronounced at higher grades of VUR (Fig. 3). They thus concluded that prophylaxis is modestly effective.

The RIVUR study (Randomized Intervention for children with Vesico Ureteral Reflux) is a new well designed study that is presently recruiting. It aims to evaluate the effectiveness of prophylaxis in children with VUR after a 1st UTI[21].

A third important and recently published VUR trial is the Swedish Reflux Study[20]. They randomised 600 patients, 66% of whom were girls who had proven dilating (Grade III-V) VUR to prophylaxis, surveillance alone or a STING (endoscopic ureteric bulking) procedure. Resolution of VUR at 2 years was 40%, 48% and 71%, respectively (P=0.0002). and UTIs recurred in 19%, 57% (p=0.0002) and 23%, respectively. The authors concluded that STING or prophylaxis is better than surveillance. Both febrile UTIs and renal scars were more common in the surveillance arm, particularly in girls.

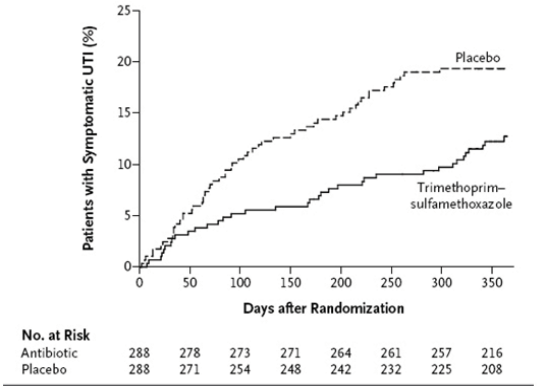

Fig. 3: Data from the PRIVENT trail showing time to symptomatic UTI of placebo vs prophylaxis[19].

The Swedish study is important, because unlike previous studies that have compared antibiotics with surgery, it concludes that there is a favourable role for the STING procedure. Endoscopic treatment has good long-term results in preventing febrile UTIs. Stenberg et al followed STING patients for 7-12 years after treatment and found a UTI incidence of only 3.4%[28].

Finally, our ability to define those children at risk of scarring remains crude. VUR is a heritable disease. In future, markers of genetic susceptibility to UTI in those with VUR will doubtless play a role. Unfortunately, while much is already known, definite markers for clinical use do not yet exist[17].

CONCLUSION

We conclude that revised investigation protocols such as the one employed at Red Cross Children's Hospital needs to be popularised, particularly the suggestion that MCUG is inappropriate after an initial febrile UTI.

Antibiotic prophylaxis provides marginal benefit for most children, particularly those with low grade VUR. It seems that, as the Swedish Reflux Study has shown; endoscopic treatment is a good choice to prevent UTIs and resultant scarring. Enthusiasm for STING in the developing world needs to be tempered by its cost. Hence there remains an ongoing role for open surgical reimplantation, particularly in Africa.

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Editorial Comment

While this manuscript does not provide new information, it is a very good review of current information for the management of vesicoureteral reflux (VUR) and how one can apply it to a specific population of patients with its own urinary tract infection and VUR characteristics.

We commend Dr. Lazarus for this concise summary of some of the contemporary issues surrounding the diagnosis and treatment of vesicoureteral reflux (VUR). Clearly, VUR is fraught with overdiagnosis and overtreatment. The classic, bottom-up approach may result in many negative, and unnecessary, VCUGs (and even ultrasounds as noted in the article). In an effort to minimize this, the top-down approach has been developed and has gained popularity. Further, there are conflicting reports on the utility of antibiotic prophylaxis as mentioned in the article. A recent commentary by Peters perhaps best summarizes the philosophical issue with our diagnosis and management of VUR—that this is not a homogenous disease upon a homogenous population (1).

Many patients with higher grades of VUR and urinary tract infections (UTI) will escape without renal scarring and many patients with lower grades of VUR may fare much worse. In other words, VUR has different risk of renal injury for different patients, irrespective of the grade. However, at this point, we cannot accurately

identify which patients will be significantly affected by VUR. It is logical that we have elected, as a society, to offer overdiagnosis and treatment as this is seen as less egregious than underdiagnosis and treatment. Ultimately, our current tools are not sensitive or specific enough to neither prevent unnecessary tests and treatments nor predict the risk of reflux nephropathy. Certainly, this is a function of the population for which these tools are used. As noted in the article, Africans have a lower prevalence of VUR. Hence, tools used in the US or Europe may result in a lower positive predictive value in Africa (and result in even higher rates of overdiagnosis and treatment). Perhaps pre-testing identification of risk factors, such as dysfunctional voiding, C-reactive protein levels during a UTI, newer imaging techniques, and other advances may increase the sensitivity or further alter newer diagnostic algorithms and decrease the overdiagnosis and overtreatment of this disease. However, this must be tailored to the population, and more specifically, the patient being evaluated.

1. Peters, C, Vesicoureteral Reflux: Seeing the Trees in the Forest. The Journal of Urology, Vol 184, Issue 1, July 2010, Pages 8-9

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