Journal of Pediatric Urology (2009) 5, 336—341

Journal of Pediatric urology

Controversies in the management of vesicoureteral reflux: The rationale for the RIVUR study☆

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Received 11 March 2009; accepted 13 May 2009
Available online 1 July 2009

KEYWORDS
Urinary tract infections;
Vesicoureteral reflux

Abstract The current management of vesicoureteral reflux (VUR) focuses on the prevention of urinary tract infections (UTI), with curative surgery being limited to those children that fail conservative measures. This is based on the assumption that UTIs are preventable with the use of prophylatic antibiotics, leading to reduction of renal scarring, and the possibility that VUR in children can resolve spontaneously.

Methods: Review of the recent literature has demonstrated a growing concern that antibiotic prophylaxis may not lead to prevention of UTIs. Additionally, data indicate that renal scarring may not be preventable with antibiotic prophylaxis or even surgical correction of VUR. An overview of all of the current controversies is presented in this paper.

Results: Does antibiotic prophylaxis lead to reduction in UTIs in children with VUR? To address this question, the National Institutes of Health have developed a randomized placebo-controlled study of children with VUR (the RIVUR Study), identified following the development of a UTI.

Conclusions: There are far reaching consequences of the results of the RIVUR Study. If antibiotic prophylaxis does not prevent UTI in children with VUR, or lead to reduction in renal scarring, does identification of VUR provide any benefits? Perhaps appropriate treatment of UTI may be all that is necessary for preserving renal function. Final answers will have to wait until the completion of this study.

Introduction

The retrograde flow of urine from the bladder to the kidneys in children has the potential to lead to the development of pyelonephritis and secondary renal injury. Management of VUR has been based on the premise that prevention of UTIs or ablation of reflux can lead to a reduction in the potential for pyelonephritis and renal

☆ The Randomized Intervention for the Management of Vesicoureteral Reflux (RIVUR) Study, Funded by the NIH/NIDDK.

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1477-5131/$36
doi:10.1016/j.jpurol.2009.05.010

scarring. Additionally, the potential for reflux to resolve spontaneously with time in many children has led to the recommendation that initial management be limited to non-operative modalities (i.e. antibiotic prophylaxis and radiographic follow-up), with surgical treatments considered in those children that develop infections despite prophylaxis or are unable to comply with prophylaxis regimens. Most of the current recommendations were derived from studies that were limited by inadequate patient numbers and/or lack of randomization. Almost every aspect of the diagnosis and management of VUR is being re-evaluated. The *R*andomized *I*ntervention for the management of *V*esico*U*reteral *R*eflux (RIVUR) Study was proposed and supported by the National Institutes of Health to address some of the questions that have been raised in the management of VUR. This was designed as a multi-institutional randomized study to determine if antibiotic prophylaxis is beneficial for the prevention of UTIs in children with VUR identified following a UTI (Fig. 1).

Controversies

Urinary tract infections

UTIs are the most frequent reason for radiographic evaluation of children to determine the presence of VUR. Such infections are seen in 2.2% of boys and 2.1% of girls younger than 2 years of age [1]. The incidence of first UTI in children younger than 6 years of age was noted to be 6.6% for girls and 1.8% for boys [2]. In a large cohort study, first UTIs were noted in 0.88% of children [3], the majority of whom were white females 2—6 years of age [3]. Only 35% of children who had a first UTI were evaluated with VCUG. Recurrent UTIs were noted in 0.11% of the total cohort. VCUG was only performed in 35% of these children. One third of children in both groups evaluated with VCUG had VUR. In a small cohort study of infants 1—12 months of age there were an equal number of male and females presenting with a first UTI [4]. All of the males in this cohort were uncircumcised. VUR was noted in 24% of infants less than 12 months of age and in 20% of infants between 12 and 24 months of age. Similar rates of VUR were noted in a cohort of Turkish children presenting with first (22%) or second (26%) UTIs [5]. Attempts to predict the potential for VUR in children after first febrile UTI using a multivariate approach [6] have had limited success when applied in clinical practice [7]. Use of procalcitonin has been shown to have some applicability in the identification of children that may have VUR following a first febrile UTI [8]. Overall specificity was only 43% [9].

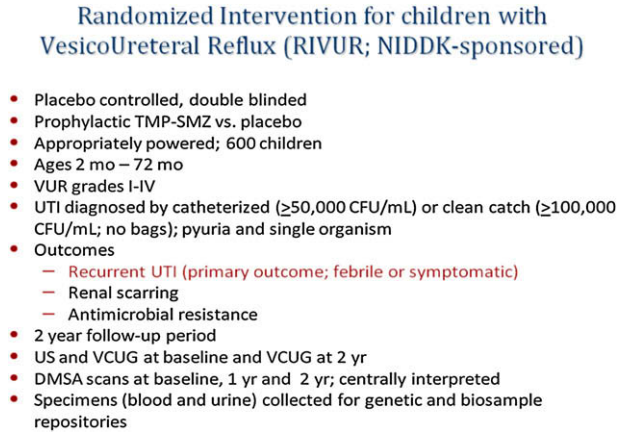

Figure 1 The RIVUR Study — clinical parameters.

Many pitfalls are noted in studies of children with UTIs. Many studies include cultures that are not collected using sterile techniques, nor correlated with urinalysis to differentiate between bacteriuria and colonization. Lack of circumcision and collection of urine specimens using bagged specimens lead to increased contamination of specimens and the potential for overestimating the incidence of UTIs.

Renal injury and/or dysplasia

VUR has been associated with renal injury; however this relationship is being debated. Abnormalities on DMSA renal scintigraphy, in a study of children < 2 years of age, were found more frequently in those with higher grades of VUR ($>$ grade 2) [10] and in those children with recurrent UTIs. Renal scarring was noted in 19% of children without VUR. Boys with severe bilateral reflux and serum creatinine > 0.6 mg/dl in the first year of life were at highest risk of the development of chronic renal disease [11]. Presence of renal scar was the most important predictor for development or progression of scarring in children with VUR [12]. A meta-analysis by Gordon et al. of 12 studies reviewing the interaction of VUR, UTI and renal scars concluded that the presence of VUR was only a weak predictor for the presence of renal scarring in children that are hospitalized for UTI [13]. Most children with UTI are managed in the outpatient setting, and the results of this study may be difficult to be extended to current clinical practice. These data were contradicted by a recent study indicating that acute changes on DMSA and progression to scar were more frequently noted in children with VUR [14]. A recent study from Thailand showed that there was a significant correlation between the presence of VUR and renal scarring; however, this study was compromised by the lack of an initial DMSA that could have excluded pre-existing dysplasia [15] (see below).

Evaluation of renal scarring in children with VUR indicates that there is a greater potential for renal scarring in refluxing as compared to non-refluxing units in the same child following a UTI [16]. Unfortunately, the diagnosis of renal scarring using DMSA can be confounded by dysplasia that can be seen in 14% of newborns with VUR prior to the development of UTIs [17]. Dysplasia was noted in 41% of renal units in infants evaluated prior to development of a UTI [18]. Hypertension is known to be a long-term consequence of renal scarring/dysplasia. A 10-year follow-up study, however, did not show this correlation in children with primary uncomplicated VUR [19]. A study of adults with radiographic evidence of reflux nephropathy noted hypertension in 38%—50% [20].

Biopsies from kidneys with reflux nephropathy showed remnant nephrons with infiltration of chronic inflammatory

cells, with some specimens indicating the presence of intrarenal reflux [21]. The required interaction between VUR and infection in the development of renal scarring was demonstrated using an experimental animal model [22].

Clinical course of VUR

The management of VUR is impacted by the potential for spontaneous resolution during follow-up. This potential for resolution has led to the concept of initial medical management and limitation of surgical correction to those patients that fail medical regimens or cannot comply with these regimens. Prevention of UTIs and renal scarring therefore remains the mainstay of the management of VUR, until resolution occurs. The potential for 5-year resolution of VUR varies from 25% to 50% between prospective studies [23]. A retrospective review of the clinical course of 735 children with VUR indicated that 57.6% of children had one UTI during the course of follow-up [24].

Diagnosis of VUR: imaging

The evaluation of the child with a UTI has typically consisted of ultrasonography, VCUG and DMSA renal scintigraphy. The optimal evaluation remains a source of debate. Increasingly there is a trend to reduce the numbers of evaluations performed.

Ultrasound is typically the first test performed following the diagnosis of a UTI. Ultrasonography was not predictive of the presence of VUR in children hospitalized for acute pyelonephritis [25]. In a study of children with UTIs evaluated with ultrasound, renal scan with glucoheptonate and VCUG, combining renal scan with VCUG captured 96.9% of all abnormalities [26]. Recommending ongoing ultrasound evaluation, Giorgi et al. [27]. noted anatomic anomalies in 32 infants (16%); however only two required surgical intervention. Jahnukainen et al. [28]. noted a 14.8% incidence of abnormalities (23 renal units), nine of which required a change in management and four surgical intervention. Hoberman et al. [29] and Zamir et al. [30], despite finding 12% and 14% abnormalities on ultrasound in children with first febrile UTI, showed that none of these altered management. The role of ultrasound in the evaluation of children therefore remains a source of debate. Perhaps this modality should be limited, such that only children 0—24 months of age who have not demonstrated a negative third trimester renal ultrasound undergo evaluation following first UTI.

VCUG has been considered the gold standard for the evaluation of VUR. Typically this is performed using fluoroscopic imaging; however, in an effort to reduce radiation exposure, radionuclide VCUG has also been utilized for evaluation and follow-up of VUR [31]. Recently, voiding urosonography has also been introduced into the imaging armamentarium [32], although utilization has been limited to a few centers. VCUG has been used to grade reflux based on classification suggested by the International Reflux Study [33]. Early performance of VCUG, within 10 days of infection, was not found to affect the performance or results of the study with equivalent numbers of patients identified with and without reflux in each of the three time indices studied [34]. Routine use of midalzolam was not found to alter identification of VUR in a randomized placebo-controlled study of children (aged 1—14 years) undergoing first VCUG [35]. Current debate however revolves around whether VCUG should be performed prior to DMSA renal scanning — the 'bottom-up' approach.

Other radiographic modalities have been used to identify the presence of VUR. The most physiologic modality is indirect radionuclide cystogram [36]. While this avoids the need for catheterization [37], there is an increased risk of false negatives using this modality [38]. Magnetic resonance voiding cystography has high specificity and sensitivity without radiation, but is an expensive modality and not widely available.

DMSA renal scintigraphy has been considered to be the gold standard for the evaluation of scarring following UTIs in children. Renal scarring has been shown to better correlate with the presence of recurrent UTIs than the presence of VUR. This has led to the consideration of performing DMSA renal scanning as the initial test for the evaluation of children with VUR. This 'top-down' approach is based on the retrospective study by Hansson et al. [39], indicating that 51% of 303 children with UTI had evidence of abnormal DMSA renal scans, and 26% (80 children) had VUR. Limiting VCU to those children with positive DMSA renal scans would permit 50% of children to avoid having VCUs. Another study, also retrospective, had very similar findings [40]. Pitfalls of DMSA scanning however include lack of conformity in performance and interpretation between various institutions and inability to differentiate between congenital dysplasia and scarring following infection.

In an effort to address some of the pitfalls with prior studies, the RIVUR study has developed a protocol that includes initial ultrasound, VCUG and DMSA renal scanning at baseline. DMSA renal scanning is repeated following UTIs and also at 12 and 24 months. Additionally, ultrasound and VCUG is repeated at 24 months at the conclusion of the follow-up period. An initial radiology pilot study was performed in which all participating institutions sent in sample studies of ultrasound, VCUG and DMSA renal scans for evaluation by a group of reference radiologists blinded to clinical parameters. The pilot tested the clarity of data transmission from the clinical sites as well as the ability to achieve consensus among the reference radiologists. All of the studies that are obtained in the course of the study are de-identified and sent to the reference radiologists using an encrypted system. The studies are reviewed by the two reference radiologists and the reading sent to the data coordinating center for the study.

Current management of vesicoureteral reflux

Initial studies demonstrated a correlation between UTIs and the presence of VUR. This led to the routine management of VUR with surgery. Antibiotic prophylaxis was also put into routine use for the prevention of UTIs. The demonstration that spontaneous resolution was possible for most cases of non-dilating VUR led to follow up becoming the primary management for lower grades of VUR [41]. The International Reflux Study was unable to show a difference between medical management and surgical correction in

children with grades III and IV VUR in the prevention of renal scarring. The International Reflux Study also set forth a grading system for VUR using radiographic VCUG that was reproducible.

Prevention of urinary tract infections

The primary reason for the use of antibiotic prophylaxis has been to reduce the rate of UTIs in children with VUR and therefore bring about a reduction in renal scarring. Many studies have attempted to determine if prophylaxis leads to an actual reduction in the incidence of UTIs. The initial study that attempted to address the utilization of antibiotics for the prevention of infections in VUR was conducted by Garin et al. in 2006 [42]. Children were randomized following a documented episode of pyelonephritis to antibiotic prophylaxis or no treatment. No difference was noted in the incidence of UTI in those patients that were provided prophylaxis as compared to untreated children. This was a small study with a higher drop-out rate in the group that was on prophylaxis due to lack of compliance. The role of voiding dysfunction and the circumcision status of males were not considered in this study. Pennesi et al. [43] also randomized a small cohort of children to prophylaxis or follow-up. As in the Garin study, no placebo control was provided. This study only evaluated children that had symptoms during the follow-up period. No difference in the incidence of pyelonephritis or renal scarring was noted. This study was compromised by the fact that specimens were obtained using bags and almost 50% of the patients were male and uncircumcised. A multi-center trial conducted by Roussey-Kessler et al. randomized 225 young children (1—3 years) to antibiotic prophylaxis versus no treatment [44]. They noted no statistical difference between the two groups in the development of UTIs. Subset analysis however did indicate a benefit of prophylaxis in boys with Grade III VUR. Methodological issues with the study included use of bags for urine collection in non-toilet-trained children, and the absence of a placebo control. Additionally, the routine screening of children, rather than evaluation limited to those with symptoms, could potentially have led to identification of asymptomatic bacteriuria or preputial colonization in male infants. The Cochrane database review by Hodson et al., comprising data from 11 studies on the management of VUR, indicated that there was no significant difference in the development of renal scarring between children treated medically and those managed surgically [45]. Although they concluded that there was no significant clinical benefit in treating children with VUR, there was a 50% reduction in febrile UTI in children that had combined management (medical and surgical). A meta-analysis of randomized controlled studies by Wheeler et al. [46]. included eight trials (859 children) that randomized children to antibiotic prophylaxis with or without surgical intervention, and sought to determine if antibiotic prophylaxis had efficacy in prevention of UTIs. This meta-analysis also did not demonstrate any benefit of antibiotic prophylaxis over combined antibiotic and surgery in the prevention of UTIs, although children in the combined treatment group did have fewer febrile infections. Only one of the trials in this meta-analysis compared antibiotics to no treatment, and did not show a difference in infection rates. All of the studies in this analysis were compromised by lack of a placebo group and by varying methods of urine collection.

Pennesi et al. studied the benefit of antibiotic prophylaxis in preventing pyelonephritis in children with grades II—IV VUR [43] diagnosed after an initial episode of pyelonephritis. Fifty patients were randomized to each arm. No difference was noted in rate of 'pyelonephritis' between the two groups. No effort was made to differentiate febrile from non-febrile UTIs in the definition of pyelonephritis. Renal scarring on DMSA was only noted in those children with higher grades of VUR (grade IV). Montini et al. [47] randomized 338 patients in an open label study, between prophylaxis and no treatment in children with VUR, and found that there was no difference between the two groups in the development of UTIs.

Some of these issues have been addressed by the RIVUR protocol (Fig. 1). Urine specimens are all collected using catheterized or clean catch specimens. Only specimens that have both pyuria and/or are positive for leukocyte esterase along with a positive urine culture (>100,000 colonies) are considered eligible for entry into the study. Circumcision status of boys is identified. All infections are identified secondary to fever or symptomatology. Only patients that are diagnosed with VUR (grades I—IV) are included in the study. Children are randomized between antibiotic prophylaxis and placebo.

The role of dysfunctional elimination syndrome

Dysfunctional elimination is increasingly being recognized as a potential source of recurrent UTIs in children. Shaikh et al. did not find a correlation between early identification of VUR or UTI and eventual development of dysfunctional elimination syndrome [48]. Snodgrass noted a significant correlation between recurrence of UTIs and the presence of voiding dysfunction [49]. VUR was noted in 20% of girls with voiding dysfunction. Breakthrough UTIs were noted in 43% of girls with VUR who also had voiding dysfunction as compared to 11% in those without voiding dysfunction. This led to a higher percentage of children with VUR and voiding dysfunction undergoing surgical correction [50]. Few prior studies have explored the effect of voiding dysfunction on the potential for recurrence of UTIs in children with VUR.

The RIVUR study identifies toilet-trained children for the presence or absence of voiding dysfunction using a standardized questionnaire. The impact of voiding dysfunction in the development of UTIs will be one parameter that can potentially be assessed.

The role of surgical management

Improvement in surgical techniques with reduction in hospital stays made surgical correction more appealing. The introduction of endoscopic regimens has also made surgical correction more acceptable to parents. Most surgical modalities are associated with a very high potential for the correction of VUR. The benefit of the surgical management of VUR in prevention of infection and scarring

continues to remain in question. The final report of the International Reflux Study indicated that at 10-year follow-up there was little difference in renal scarring between the medical and surgical groups [51]. There was a lower incidence of febrile infections in those children who had surgical correction as compared to those in the medical arm. Options for surgical management include endoscopic, laparoscopic, robotic and open procedures.

The introduction of approved injectable agents has led to a resurgence in the use of endoscopic management of VUR. Early success with the use of polytetrafluoroethylene (Teflon) paste [52] was tempered by concerns of particle migration and restrictions imposed on use in the United States. Other injectable agents were found to have limited long-term success for the correction of VUR [53]. The introduction of the approved injectable agent dextranomer/hyaluronidase (Dx/HA) [54] has led to widespread acceptance of endoscopic treatment for management of VUR. Studies have indicated that there may be a reduction in the number of infections following successful reflux correction with Dx/HA when compared to pre-procedure numbers [55]. Patients presenting with recurrent infections following successful initial Dx/HA injection were found to have late recurrence of VUR [56]. While considerations have been raised to use Dx/HA as a primary modality for the management of VUR, there are no data to indicate that this is appropriate and it does not appear to be cost effective.

Open surgical management has been associated with very high success rates for the ablation of reflux; however, no difference has been noted in the rate of recurrence of UTIs or progression of renal scarring, although there was a reduction in the incidence of pyelonephritis.

The RIVUR study is not designed to analyze surgical management of VUR. Once the primary question regarding the benefit of antibiotic prophylaxis is answered, further studies will be forthcoming to study the benefit/or lack thereof of surgical management. Most clinicians would agree that the current indications for surgical management remain: resolution of high-grade VUR (Grade V) following UTIs, inability to maintain prophylaxis in children that are on antibiotic regimens, presence of breakthrough infections despite appropriate prophylaxis, and the progression or development of renal scarring during the course of follow-up.

Conclusion

The paucity of well thought-out randomized studies on VUR in children has led to continued debate on the correct algorithm for evaluation and management. The RIVUR study is recruiting a numerically appropriate cohort of children ($n = 600$) to answer the fundamental question in the management of VUR — does antibiotic prophylaxis lead to prevention of UTIs and secondarily renal scarring? It has been designed to overcome some of the identified problems with prior cohort studies that have purported to determine the answer to this question. Development of the protocol has led to identification of variations in radiologic testing as well as practice patterns around the country. It is hoped that the final report of this study will help to set down the initial steps in the algorithm of the evaluation and management of children with VUR.

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