

Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR): Background Commentary of RIVUR Investigators

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ABSTRACT

Because of the frequency of urinary tract infections in children, off-label use of antimicrobial prophylaxis is often the usual treatment of children with vesicoureteral reflux, and such use is increasingly being called into question; hence, a definitive study to determine the value of antimicrobial prophylaxis with regard to the recurrence of urinary tract infection and the incidence of renal scarring is essential. The currently recommended follow-up procedures (repeated urine cultures, renal and genitourinary imaging, antimicrobial therapy and prophylaxis, as well as other factors including cleanliness, adequate bladder and bowel emptying, and compliance with protocols) are expensive (in terms of time, attention to detail, and cost) and cumbersome. Such recommendations should be evidence-based. *Pediatrics* 2008;122:233–239

BECAUSE OF THE frequency of urinary tract infections (UTIs) in children with vesicoureteral reflux (VUR), the need exists for a well-designed and appropriately powered study that can determine the effectiveness of antimicrobial prophylaxis on preventing recurrences of UTI and on decreasing the incidence of renal scarring. Because the currently recommended follow-up studies, including repeated urine cultures, renal and genitourinary imaging, antimicrobial therapy, and antibiotic prophylaxis as well as compliance with protocols, are costly and cumbersome, these recommendations ought to be based on actual evidence. Because of the relatively low prevalence of renal scarring, the cost of identification of VUR, and the potential problems of long-term antimicrobial prophylaxis and/or surgical correction of VUR, a carefully designed and sufficiently large prospective clinical trial to assess the effectiveness of current evaluation and therapeutic strategies seems warranted. We propose a multicenter, randomized, placebo-controlled, double-blind study to determine if, in the setting of prompt evaluation of UTI symptoms and early therapy of culture-proven UTI, administration of daily antimicrobial prophylaxis is superior to daily placebo in preventing recurrent UTI and renal scarring in children aged 2 to 72 months who have been diagnosed with grades I to IV VUR after an initial episode of UTI.

THE LINK BETWEEN UTI AND VUR: CONTEMPORARY ISSUES AND RATIONALE FOR THE RANDOMIZED INTERVENTION IN CHILDREN WITH VESICOURETERAL REFLUX (RIVUR) TRIAL

UTI remains the most frequently occurring serious bacterial infection during childhood.¹ Estimates of the cumulative incidence of UTI in children <6 years old (3%–7% in girls and 1%–2% in boys) suggest that between 70 000 and 180 000 of the annual US birth cohort will have a UTI by the age of 6 years.² UTIs have been considered to be the principal cause of permanent renal parenchymal damage and scarring in children, especially those with VUR.³ VUR results in urine passing up the ureter in a retrograde fashion. The extent of passage up the ureter is categorized hierarchically, with grades III, IV, and V being defined by progressive dilatation and distention of the renal pelvis.^{3,4} Because VUR is found in 30% to 40% of children with a UTI, the current standard of care has included performance of an imaging procedure to assess the presence and extent of reflux.^{5,6} This strategy depends on the hypothesis that reflux, especially of higher grades, increases the risk of recurrent UTIs and renal scarring, with associated sequelae in later life of proteinuria, hypertension, eclampsia, and end-stage renal disease (ESRD).^{2,5,7–9} Despite the recom-

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Key Words

clinical research/trials, urinary tract infections, vesicoureteric reflux, VUR

Abbreviations

UTI—urinary tract infection
VUR—vesicoureteral reflux
ESRD—end-stage renal disease
DES—dysfunctional elimination syndrome
DMSA—dimercaptosuccinic acid
APN—acute pyelonephritis

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mendation that all children with a UTI be evaluated for reflux, there is a failure to do so in contemporary populations. In a recent survey of infants <1 year of age who had febrile UTIs, up to 40% were not evaluated for reflux as recommended by the American Academy of Pediatrics.¹⁰ This suggests that even at this point in the United States many children with reflux remain undiagnosed after a UTI.

The causal relationship between reflux and pyelonephritic scarring was challenged recently by long-term studies that demonstrated that renal scarring can occur in children without VUR and that not all children with VUR, including those with higher grades of reflux, have renal scars.^{1,11} In addition, monogenic (and even polygenic) conditions result in reflux and progressive renal damage, often as a component of an identified syndrome; these can be viewed as separate from primary reflux.^{12,13} Reports from the 1960s and 1970s, when reflux was recognized less frequently, revealed that pyelonephritic scarring was the etiology of 50% of the cases of hypertension and 30% of cases of ESRD in children.^{14–17} These rates have been reduced considerably in some contemporary populations as a result of widespread recognition and treatment, with scarring now accounting for 5% of children with hypertension and significant renal impairment in this country.^{18,19} This has not been the case worldwide, however. Craig et al²⁰ have shown that there has been no decrease in the incidence of reflux-related ESRD in Australia and New Zealand over the last several decades. Approximately 14% of all children enrolled in their ESRD registry had reflux as a cause, and this has remained constant from the 1960s through the 1990s. They postulated that the identification of reflux had no impact on the rates of renal failure. It was assumed by the authors, however, that primary care physicians have assiduously evaluated children for reflux in recent decades, but this may not be true, as shown above. Reflux remains a leading cause of chronic renal failure in children and young adults in Italy, accounting for 25% of all cases.²¹ Most of those patients had greater than grade III reflux, and 76% were boys. Many of the boys were born with high-grade reflux and renal dysplasia, and it is possible that they would have progressed to renal failure despite any type of postnatal management. Again, it is also possible that the relatively high rate of reflux-related ESRD may be related to failure to diagnose reflux after an initial UTI in many children.

More importantly, studies comparing the effectiveness of combined surgical correction and antimicrobial prophylaxis to antimicrobial prophylaxis alone have not demonstrated differences in rates of renal scarring.^{1,2,5,9,11,22} Other concerns about current diagnostic and therapeutic strategies include the cost and potential psychological harm of studies to detect VUR and its follow-up to resolution^{5,11,22,23} and the development of antimicrobial resistance with long-term prophylactic antibiotic use.^{24,25} Doubts have arisen concerning the role of VUR in renal scarring and the efficacy of current therapeutic strategies in comparison to prompt evaluation and treatment of UTI.^{2,7,8,26}

Because of the low prevalence of renal scarring, costs of identifying children with VUR, and the potential problems of long-term antimicrobial prophylaxis and/or surgical correction of VUR, the need exists for a carefully designed and adequately powered clinical trial to assess the effectiveness of current evaluation and therapeutic strategies.^{1,23} In our current trial, we propose a multi-center, randomized, placebo-controlled, double-blind study to determine if, in the setting of prompt evaluation of UTI symptoms and early therapy of culture-proven UTI, daily antimicrobial prophylaxis is superior to daily placebo in preventing recurrent UTI and renal scarring in children aged 2 to 72 months who have been diagnosed with grades I to IV VUR after an initial episode of UTI.¹²

BACKGROUND

Studies for >50 years have suggested a link between recurrent UTI, VUR, and renal parenchymal scarring.^{3,4,7–9,25} Renal scarring has been associated with proteinuria, hypertension, failure of renal mass to grow, progression to chronic kidney disease, and, ultimately, to ESRD that requires renal replacement therapy.^{4,24,27,28} Under this model of chronic renal failure, long-term antimicrobial prophylaxis administration, surgical correction of VUR (such as ureteral reimplantation or endoscopic injection of a biocompatible material to diminish the size of the lumen of the ureterovesical orifice), or both have been used to prevent the damage related to an inflammatory response after retrograde reflux of infected urine to the ureter to the renal pelvis (Fig 1).

Several findings have emerged that strongly question the validity of this hypothesis. First, review of the studies that formed the basis for our current strategies for preventing UTI- and VUR-related renal scarring reveals an absence of strong supportive evidence, with few ran-

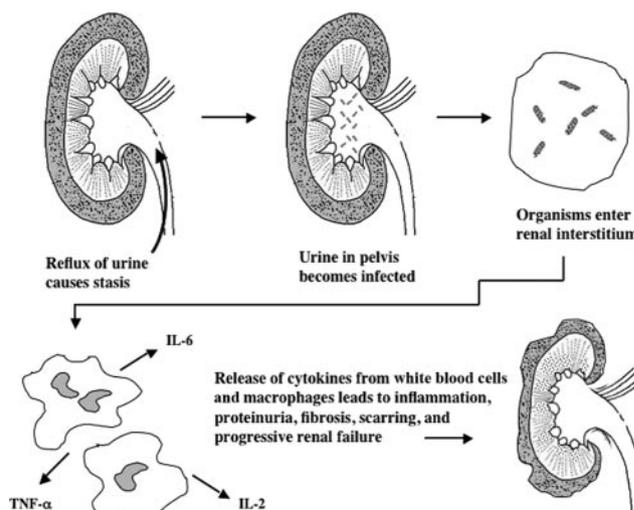


FIGURE 1

Theoretical model showing how urinary stasis caused by VUR leads to bacterial growth in the renal parenchyma. Macrophages and leukocytes migrate to the interstitium and secrete proinflammatory cytokines, resulting in fibrosis and scarring with a progressive decline in renal function and the development of proteinuria and hypertension. In reality, only a minority of children with primary VUR develop scarring. IL indicates interleukin; TNF- α , tumor necrosis factor α .

domized, controlled trials.^{5,11,22,23,29} Second, antimicrobial prophylaxis has been shown to be superior to placebo in terms of prevention of recurrent infection in only a limited fashion, and the value of antireflux surgery is even less certain.^{1,2,5} The finding of renal scarring in children with recurrence of UTIs in the absence of VUR raises issues concerning the model.^{1,11} Long-term studies have shown that the proportion of children receiving antimicrobial prophylaxis or surgery who develop new scarring is actually quite low, and most children do not progress to chronic kidney disease.^{1,4,5,9}

Additional issues influence the model. A certain number of children with VUR and recurrent UTIs will have chromosomal, monogenic, or polygenic conditions, which may include embryonic malformation of the kidney, renal hypoplasia, dysplasia, or obstruction.^{12,13} Antimicrobial resistance in the patient and the community raises concerns about the safety of antimicrobial prophylaxis in both UTI and acute otitis media studies.³⁰⁻³²

VESICoureTERAL REFLUX

VUR, retrograde urine flow from the bladder to the ureters, is the most common functional abnormality of the urinary tract in children.^{5,11} Primary VUR is characterized by short mucosal tunnel length, as opposed to secondary VUR, in which reflux is the result of increased bladder pressure from a neurogenic bladder, outlet obstruction, or other vesicular anomalies. The proposed study will address only primary reflux.

Over the past 3 decades, it has become apparent that ~30% to 40% of children investigated by imaging studies after a UTI show evidence of VUR.^{4,6,9} An international grading system of reflux has been established that proceeds from grade I (reflux up a nondilated ureter) to grade V (massive reflux with marked ureteric dilatation and distention of the pelvis with concavity of the papillae or papillary flattening). These grades are well described and involve increasing degrees of reflux, dilatation, and cupping of the papillae.^{3,4,6,9,27}

VUR is also seen in asymptomatic family members of an index case at rates of from 20% to nearly 50% penetrance. Such VUR is found in successive generations without particular influence of consanguinity. Other genetic conditions, to be discussed below, are associated with VUR and recurrent UTIs.²⁸

Another issue for consideration is that primary VUR may be discovered during follow-up investigations for prenatal ultrasound findings or after a UTI.^{8,26,31} Because our interest is in patients with primary rather than secondary VUR, the timing of the discovery of reflux is less important. Put differently, all primary VUR exists on an embryologic basis.^{13,26} The main differences between prenatal and postnatal disease are therapeutic approaches, including the choice of antimicrobial agents, the organisms encountered, and a greater spontaneous remission rate in younger children. Reflux nephropathy is an appreciable cause of progressive renal failure leading to a need for renal replacement therapy. Thus, the model of infection, detection of reflux, and treatment is based on many older studies that are smaller and non-randomized and may include secondary reflux.

Although numerous studies have examined the importance of antireflux surgery, only a few studies have been of sufficient duration and size to permit valid statistical analysis.^{5,11,22} In general, these studies examined open vesicoureteric reimplantation and have not evaluated endoscopic ureteral surgery. Some of the earlier studies, which supported the need for treating VUR either surgically or medically, had significant methodologic limitations and did not particularly address the question for the majority of children who exhibit low-grade reflux. Most of these investigations were uncontrolled, used intravenous pyelograms to assess for scars, and did not all use the international scale to grade VUR.³³⁻³⁵ Yet, these studies form the basis of all contemporary therapy. Large uncontrolled studies of children placed on long-term prophylaxis have unquestionably shown, however, that the rate of new scar formation after breakthrough infection is extremely low: <3%.^{36,37} In the later decades of the 20th century, the greater debate was between those who would treat patients prophylactically versus those who would correct the reflux surgically. Therefore, controlled trials such as the International Reflux Study in Children and the Birmingham Cooperative Study were designed to compare the efficacy of prophylaxis to surgery.^{38,39} The International Reflux Study in Children looked specifically at children with grades III and IV (mostly IV) reflux. Both studies showed that surgery and prophylaxis were equivalent in preventing new renal scars or pyelonephritis in children with reflux. Because none of these studies included a placebo or "observation-only" arm, the question has also been raised as to whether surgery or antimicrobial prophylaxis has any effect on renal scarring in children with VUR diagnosed after a UTI.

VOIDING DYSFUNCTION AND REFLUX

Neurologically normal children can demonstrate temporary, but often significant, aspects of lower urinary tract dysfunction during toilet-training years. It is assumed that this dysfunction is a result of faulty learning or habituation. These children tend to hold both their urine and bowel movements for an excessive amount of time as they attempt to toilet train.⁴⁰ They do not appropriately relax their perineal sphincters while voiding or defecating. As a result, they are constipated and do not empty their bladders completely.⁴¹ They have what is termed the dysfunctional elimination syndrome (DES). They void at higher-than-normal voiding pressures, because voiding occurs when the urinary sphincter is not appropriately relaxed.⁴² They also tend to have unstable, "hyperreflexic" bladders that contract at lower-than-normal volumes. These children often have recurrent UTIs with or without reflux, along with urinary incontinence and fecal soiling.

Children with DES and VUR form a special subset. It has been shown that these children have a higher incidence of breakthrough infection while on prophylaxis, more renal scarring, a lower incidence of spontaneous resolution with growth, and a higher failure rate after antireflux surgery.⁴³⁻⁴⁵ DES can be assessed historically by questionnaire or toileting diary.⁴⁰ In particular, fam-

ilies are queried regarding voiding frequency, urinary incontinence, constipation, and fecal soiling. Voiding dysfunction can also be confirmed by invasive urodynamic testing.^{42,46} Many are reluctant to perform these tests on a regular basis in all children with reflux and rely mainly on a clinical history. Based on a questionnaire, a dysfunctional voiding symptom score has been developed that is valid and reproducible.^{47,48}

The etiologic relationship between reflux and DES in the older toilet-trained child is not well established, however. It is not known if reflux in these children results from congenital valvular deficiency or is secondary to abnormal voiding dynamics with a normal ureterovesical junction. In one study, the overall rate of DES in refluxing and nonrefluxing populations of toilet-trained children was similar, although the risk of having dysfunctional voiding in the group with both UTI and reflux was greater.⁴⁹ It was shown in a cohort of infants diagnosed with reflux at <1 year of age that they did not have a greater incidence of dysfunctional voiding as they aged as compared with an age-matched population without reflux.⁵⁰

ROLE OF INFECTION AND VUR IN SCARRING

At least 1% of boys and 3% to 5% of girls will experience at least 1 UTI during childhood: of these, 30% to 50% are likely to have a recurrence.⁸ Permanent renal scarring after pyelonephritis is detected 5% to 20% of the time when children are evaluated with intravenous urography and up to 40% of the time when evaluated by a dimercaptosuccinic acid (DMSA) renal scan.^{1,5} The finding of scarring increases with each episode of pyelonephritis.²⁵ The conventional view is that the incidence of scarring falls after the fifth to seventh birthday, even with new infections, but in a large study by Benador et al,⁵¹ the frequency of scarring was the same in children aged 1 to 5 years as it was in children older than 5 years. Rushton et al,⁵² in a now classic study, emphasized that new renal scars form less frequently in kidneys with VUR than those without. In a meta-analysis of randomized, controlled trials of antimicrobial agents and antireflux surgery for VUR,^{11,22} Wheeler et al concluded that "it is uncertain whether the identification and treatment of children with VUR confers clinically important benefit."²² It also seems that scarring may be identical in refluxing and nonrefluxing units,^{3,11,22} which challenges routine initiation of antibacterial prophylaxis after detection of VUR in all patients.⁵³

Another major problem with the published literature is the aggregation of cases with secondary VUR attributable to genetic causes with primary VUR. A number of malformation syndromes, some with a recognizable inheritance pattern, can be associated with VUR, infection, and scarring.^{12,13} Among these are VATER-VACTERL (vertebral, anal, cardiac, tracheoesophageal, renal, limb) syndrome and other syndromes with a variety of renal malformations including renal agenesis, dysgenesis, horseshoe kidney, a duplex pelvis, hydronephrosis, and cloacal anomalies.^{12,13} Some of these disorders are chromosomal, and others involve mutations in developmental genes (Tables 1 and 2). In a series of 317 children with anorectal

TABLE 1 Representative Syndromes That May Display VUR, Scarring, Recurrent Infection, and Progressive Renal Disease^{11,20}

VATER-VACTERL syndrome (vertebral, anal, cardiac, tracheoesophageal, renal, limb) association
Townes-Brock syndrome (<i>SALL1</i> mutation)
Cat eye syndrome (tetrasomy, chromosome 22)
Casamassima-Morton-Nance syndrome
Renal coloboma syndrome (<i>PAX2</i> mutations)
Branchio-oto-renal syndrome (<i>EYE1</i> mutation)
Frasier syndrome (<i>WT1</i> mutation)

TABLE 2 Renal and Bladder Variants Resulting in VUR^{11,20}

Renal dysplasia
Renal hypoplasia
Obstructive uropathy
Bladder changes in function
Bladder changes in neurologic status
Bladder exstrophy

malformations, 138 had associated renal anomalies and 27 had VUR. Mutations of developmental genes, including *PAX2*, *EYE1*, and *WT-1*, can result in syndromes with reflux, scarring, and reflux nephropathy.¹²

THE CHARACTERIZATION OF SCARRING

Renal scarring is the consequence of focal areas of inflammation with massive cytokine release from tissue macrophages and lymphocytes.⁵ Fibrosis is another postinfection finding. Other features are renal cortical thinning and evidence of microalbuminuria.^{1,22} In all series, a small number of children go on to have significant hypertension and ESRD.

BACKGROUND TO THERAPY

The use of antimicrobial agents to reduce recurrent UTI dates back to the 1940s and 1950s. The now classical studies of Smellie and colleagues^{6-9,22,25,27} form the most compelling reason to consider antimicrobial prophylaxis. Goals of antimicrobial therapy and prophylaxis include (1) preventing or reducing the number of recurrent UTIs and (2) reducing the incidence of scarring. Again, this set of assumptions has come under criticism because of many of the facts listed previously (Table 3).

BACKGROUND TO IMAGING STUDIES

A number of imaging techniques have been used to evaluate children with UTIs. Radiographic voiding cystourethrogram remains the gold standard for identification and evaluation of VUR. Renal ultrasound identifies hydronephrosis but is insensitive to identifying renal scarring. A number of procedures and tests have been used to try to localize the site of UTI to the upper (acute pyelonephritis [APN]) or lower (cystitis) urinary tract. An acute-phase response consisting of elevated peripheral white blood cell count, erythrocyte sedimentation rate, and C-reactive protein and procalcitonin levels were used in several studies to indicate infection of the

TABLE 3 Issues Difficult to Reconcile With the UTI-VUR Model^{11,20}

The percentage of patients with recurrent UTI and reflux who develop scarring is quite small.

In 1 small trial comparing prophylaxis with no therapy for recurrent UTI, no significant differences in risk for UTI or renal damage were found.

Many children, even those with high-grade VUR, do not develop renal scars.

Patients without VUR who have recurrent UTIs can develop scars.

Assuming a UTI rate of 20% for children with VUR on antimicrobial therapy for 5 y, 9 reimplantations would be required to prevent 1 febrile UTI.

Most trials evaluating the value of antimicrobials or surgery (open or endoscopic) are statistically underpowered, and valid conclusions are impossible to make.

Many older studies include patients with secondary causes of VUR and genetic syndromes.

The increasing emergence of organisms resistant to standard antibiotics is rising, which makes prophylaxis increasingly difficult to justify.

In a Cochrane analysis based on 10 trials involving 964 evaluable children, the authors indicated that it was uncertain whether the identification and treatment of children with VUR conferred any benefit.

upper urinary tract. However, as noted in a review article by Rushton et al⁵² and editorials by Andrich and Majd,⁵⁴ Conway and Cohn,⁵⁵ and Hellerstein,⁵⁶ children who have a first UTI accompanied by fever and toxicity cannot be diagnosed reliably as having APN on the basis of clinical signs and symptoms or laboratory parameters alone.

Currently, DMSA scintigraphy is the imaging agent of choice for the detection and evaluation of APN and renal cortical scarring in children. Using strict histopathologic criteria in the refluxing infected piglet model, DMSA renal scans have been found to be highly sensitive and specific for the detection and localization of APN.^{52,57} The DMSA scan also has shown higher sensitivity and specificity than intravenous pyelography in documenting renal scars in several clinical studies and has shown good correlation with histopathology in animal data.⁵⁸⁻⁶² Consequently, DMSA renal scintigraphy provides a unique opportunity to study the progression of renal damage and functional loss from the initial insult of APN to the subsequent development of irreversible renal scarring.⁵² Accordingly, DMSA renal scanning is currently the gold standard for identifying renal parenchymal changes, including scarring.^{52,54-56} As such, DMSA renal scans will be used in the National Institutes of Health RIVUR study as the outcome measurement for the detection and semi-quantification of both preexistent and newly acquired renal parenchymal damage secondary to UTIs in children with grades I to IV VUR.

POTENTIAL HARM OF CURRENT MANAGEMENT OF VUR

Concerns exist regarding the potential harm of current diagnostic tests and therapeutic approaches. Tests for defining reflux, its nature and extent, include voiding cystourethrography and radionuclide cystography. Major concerns are as follows.

- A. Imaging: problems include cost and the long-term effect of repeated exposure to ionizing radiation.
- B. Antimicrobial agents: the daily administration of an antimicrobial medication is problematic for several reasons:

1. strains of common urinary tract pathogens are becoming increasingly resistant to traditional agents used for treating UTIs^{1,30};
 2. resistance leads to the use of other agents and classes of antimicrobial agents, which may be costlier, are not fully tested in younger children, may be excreted in sites other than the renal parenchyma, and have limited antibacterial spectra²⁸; and
 3. questions remain about the optimal length of antimicrobial prophylaxis and the need for/frequency of urine culturing.^{5,28}
- C. Length of follow-up: this is a complex issue with myriad unanswered questions.² After infancy, boys experience far fewer recurrences of UTI. In general, new scarring does not occur after the age of 5 to 7 years but, as noted, can occur in the absence of VUR. Does the risk of antimicrobial resistance outweigh the possibility of infection and the even smaller risk of scarring?^{1,5}
- D. Psychological: the process of inserting a urinary catheter into the urethra of a young child, followed by putting the child under a radiograph machine on a hard table, is clearly a source of psychological stress and the cause of tears, nightmares, and retained memories. If these tests are of only marginal, or no, value, then perhaps they should not be performed.^{1,11,22,63}

NEED FOR A WELL-DESIGNED STUDY

To date, a small number of studies in children and numerous larger studies in adults have indicated that antibacterial prophylaxis can reduce the number of recurrent UTIs.^{5,11,22} Although this could indicate that randomized, prospective, placebo-controlled trials (in children with VUR diagnosed after UTI) are not indicated, this is not the case. As succinctly stated by Craig et al in their commentary on clinical trials in children, "We do not simply need more studies. We need the right studies done right."²³ In May 2003, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored a strategic planning meeting to assess the need for and feasibility of conducting clinical trials in children diagnosed with VUR. The need for definitive research in 3 areas was identified: (1) resolution of conflicting data related to use of antimicrobial prophylaxis in a placebo-controlled trial that includes assessments of dysfunctional voiding, pyelonephritis, and renal scarring; (2) comparison of an endoscopic injection with a bulking agent with open repair; and (3) comparison of a preemptive surgical intervention with use of antimicrobial prophylaxis. The RIVUR trial is an outgrowth of this NIDDK planning meeting. To accomplish the first charge, children with a resolved first febrile or symptomatic UTI who have grades I to IV VUR will be randomly assigned to receive placebo or an antimicrobial prophylaxis with a primary end point of recurrent UTI and a secondary end point of renal scarring. We intend to study children with primary VUR recruited after their first occurrence of a UTI. We anticipate randomly assign-

ing 600 children to antimicrobial prophylaxis or placebo treatment arms. Children with urinary tract obstruction, genetic syndromes, chromosomal syndromes, and complex anomalies that influence bladder function and urinary flow will be excluded, in part because many of these children have secondary or obstruction-related VUR.^{12,13} Each child will be followed for at least 2 years, and both infection rates and scarring will be monitored. Such a study should have the statistical power to answer whether antimicrobial prophylaxis protects against these outcomes.

CONCLUSIONS

Because of the frequency of UTIs in children, off-label use of antimicrobial prophylaxis is often the usual treatment of children with VUR, and such use is increasingly being called into question; hence, a definitive study to determine the value of antimicrobial prophylaxis with regards to the recurrence of UTI and the incidence of renal scarring^{1,20} is essential. The currently recommended follow-up procedures (repeated urine cultures, renal and genitourinary imaging, and antimicrobial therapy and prophylaxis, as well as other factors including cleanliness, adequate bladder and bowel emptying, and compliance with protocols) are expensive (in terms of time, attention to detail, and cost) and cumbersome. Such recommendations should be evidence-based.⁵³

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