Assessing Patient Risk from VUR

FROM THE EDITOR

Anthony A. Caldamone, M.D.

John Woodard once said:

As one looks over the last 30 years of reflux history, it is ironic that urologists have become so expert at its surgical correction before understanding so much of its natural history and true clinical significance.

I was surprised to learn that John said this in 1983. How prophetic! One could make a cogent argument, as heretical in pediatric urology circles as it may seem, that the brilliantly designed and reproducible Politano-Leadbetter reimplantation inhibited our ability to understand the true risk of VUR. We have assumed that every child with VUR possess a significant risk for renal damage. After you read this issue of DPU, I think you will agree that the only way to properly manage VUR is by an individual game plan and not by generic algorithms based on grade and age. These contributors are pushing us to a new understanding of VUR and renal damage.
Several recent RCTs testing continuous antibiotic prophylaxis versus placebo or no treatment can be summarized as finding daily antibiotics are less effective for preventing subsequent UTI than previously thought. Furthermore, analysis of the no treatment arms shows recurrent infection is also less common than assumed, occurring in only 42% of girls with grades 3 and 4 reflux during 2 years follow-up in the series reporting the greatest prevalence of additional infection.

Together these observations suggest most children with febrile UTI and VUR do not have pyelonephritis, do not form renal scars, and will not have another febrile infection in the next year or two. Consequently, the traditional practice of antibiotic prophylaxis versus endoscopic injection versus reimplantation for all children with reflux has little evidence basis. Citing lack of scientific evidence that current treatment algorithms positively impact the health of children, even the need for imaging, especially cystography, after UTI is increasingly questioned.

If we previously over-treated some patients, today pediatric urologists are concerned nihilism regarding UTI in children will result in avoidable damage to at least some. Trying to balance both new evidence regarding antibiotic prophylaxis with the risk a pendulum swing towards no imaging or treatment by primary care providers may cause harm, the second AUA Reflux Guidelines Panel concluded that observation without antibiotics is an option for some patients, and that clinicians have to take into account perceived risks to the individual child when recommending treatment plans.

So how should urologists weigh risks and then make therapeutic decisions today? Despite proposed changes in imaging protocols, most children still have cystography ordered by their primary physicians after UTI and then present to urologists for management. Accordingly, this Dialogue will focus on assessment of the child with known reflux and UTI.

Craig Peters will begin the discussion summarizing how and why the Guidelines Panel arrived at its decision to include no treatment as an option for reflux, and to which patients it was thought to be best apply. Chris Cooper describes an internet-based model that incorporates additional factors with reflux grade to predict the odds ratio for VUR resolution within 2 years.

Tony Caldamone and his co-authors move the discussion from likelihood for reflux resolution to presumed risk for renal scarring, and then compare management among 9 pediatric urologists.

Prompted by literature review on the Guidelines Panel, 2 years ago we started a prospective observational study in Dallas using DMSA renography 3 months or longer after UTI to better understand renal scarring. Nicol Bush reports our findings and discusses their potential use for determining treatment options.

**2010 AUA VUR Guidelines**

The American Urological Association initiated a revision of the 1997 Guidelines on Pediatric Vesicoureteral Reflux and the results of that 5-year effort were published in late 2010. While clearly based on the initial Guideline findings and conclusions, the recent revision made significant changes in recommendations for VUR management based upon both new data and an evolving perception of the clinical implications of VUR. This comment will summarize the strategy behind the new guidelines and the major changes in thinking that are present within them.

The task of the AUA Reflux Guidelines Panel (see list of members below) was to develop clinical guidelines based on data wherever possible, and expert opinion as needed, for the management of VUR in children. This assumed the diagnosis of reflux, and the panel did not review diagnostic imaging strategies following UTI since it was outside the scope of our mandate. This important issue is currently under review by the AAP to develop new guidelines. The panel chose to stretch the guideline process by addressing two screening questions (sibling screening and prenatal hydronephrosis), largely because they were a constant clinical question and because they were manageable in terms of data.

As a further evolution from the prior Guideline, the panel sought to address three clinical scenarios in VUR considered important and distinct. This introduces the first and obvious element of risk assessment. The panel separated clinical management of the 1) infant with VUR, 2) the child with VUR and no abnormalities in voiding and 3) the child with overt voiding abnormalities (termed Bladder and Bowel Dysfunction or BBBD). By separating these groups, recommendations were able to be somewhat more specific to the patient at hand. While the literature did not always permit clear separation of outcomes based on these factors, a large body of data nevertheless could be generated.

The guideline process is not simply a literature review, and while it has significant limitations and flaws, it is the best available mechanism to synthesize robust data from a body of literature that is quite heterogeneous in terms of quality, reporting structure and utility.

Briefly, the Panel conducted a detailed literature search that was broadly cast. Abstracts were double reviewed to determine suitability for the specific topics of interest, and any rejected article was categorized as to the reason. A second level of selection identified articles with potentially useful data, and each was then screened for extraction by panel members. During this process many articles were found to be unusable, largely because outcomes were not linked to clinical characteristics of the study patients. Those articles with suitable data were fully extracted into subgroups based on clinical criteria and entered into a database. The database was thoroughly screened for errors and the data conditioned by looking for outliers, or inconsistencies, all of which were examined and resolved on consultation. Final acceptance of data was based on Panel review and consensus.

An assessment of the quality of the data extracted was next performed, looking for heterogeneity (if there is too much scatter in results could this be due to identifiable factors - what effect would eliminating an outlier result have on overall conclusions?) and the possibility of publication bias. We also rated all studies with a standard quality score and examined whether their conclusions were influenced by quality.

Analysis was then undertaken using a variety of statistical models (continued on next page)
to permit merging data to derive stronger statistical conclusions. The data are typically presented as Forest plots where variation can be seen as well as the cumulative results. Another means to analyze data are ecological plots. This approach graphs study results based on one characteristic of the population, such as the incidence of UTI in the whole population, as correlated to the incidence of renal scarring, for example. These types of data presentation offer better visualization of associations between clinical parameters than simple averages or correlations. With large numbers of studies overall trends may be identified, even when there is a large degree of heterogeneity in the data.

From these relationships, the Panel attempted to derive answers to a series of critical questions that drive our clinical decision-making. These questions included whether reflux increases the risk of renal scarring when a UTI occurs, and whether BBD affects the risk of UTI in VUR. From these relationships, the panel then attempted to make clinical guidelines for VUR management.

The AUA uses strict terminology in its guidelines, which includes “standards”, “recommendations”, and “options”. A standard is the strongest guideline and is based on clear data indicating the best approach. A recommendation is less strong and is based either on data that is less clear, or upon expert opinion in some situations. Options indicates that data are available indicating more than 1 strategy may be equally effective, and are important in that they clearly state an approach is justified and acceptable.

If a treatment is not included as an option then there are limited data to support it, as is the case with laparoscopic treatment of VUR at this time. Similarly, there was insufficient data to include endoscopic injection as an option in the 1997 Guideline, which became a significant issue when insurance companies refused payment for the procedure. The AUA was able to convince one large company that its omission in the 1997 Guidelines was only because there were no data then to permit analysis and the company changed its policy.

The Guidelines attempt to present its various recommendations along a clinical pathway that might be followed in a child from diagnosis to discharge. They reflect a large amount of data, but also indicate significant gaps in our knowledge on VUR. In general, a conservative approach was taken to avoid excessive risk-taking. The key elements that have emerged from this process and will hopefully serve as a foundation for further evolution of VUR management include:

1. recognition that continuous antibiotic prophylaxis (CAP) is not always needed for safe management of the child with VUR. The impact of BBD in recurrent UTI and reflux behavior, 3) the importance of family education and preferences, and 4) need for a long-term follow-up plan. These elements may seem obvious to the experienced practitioner, but it was clear to the Panel that this is not consistently so in the real world. These elements can be seen to be closely intertwined in the care of the child with VUR, and if that intertwining is recognized and acted upon, the child with VUR will be well cared for.

Data supporting the use of CAP for VUR are highly variable. While this has been the standard approach for VUR since the early 1970s, there were insufficient data to assess its efficacy in the 1997 Guideline. Recent studies reporting on its efficacy were first published after the new guidelines process was underway, but were considered sufficiently important that the Panel insisted that they be included. This meant delaying the conclusion of the project.

Nevertheless, recent series from Australia and Sweden could not be included in the database. Interestingly, these two studies did show a clinical benefit to CAP with VUR, although of variable degree. The study by Roussey-Kesler, et al, found CAP was beneficial in boys with Grade III VUR, while in the Swedish study there was a clear benefit to CAP in girls with Grade III reflux. However, other studies from Europe that did not show significant benefit were all multi-center, prospective trials of high quality.

None-the-less, all these reports clearly demonstrate that many patients with VUR will not benefit from CAP. What is missing are the clinical criteria to identify those children. But we can infer from this other guideline data. The child with BBD, a history of recurrent UTIs, and the presence of renal scarring is at greater risk for further UTI and possible renal injury than the child with no BBD, a first-time UTI and normal kidneys. These are the fundamental criteria used in my practice for selecting the child in whom CAP will be of little benefit versus the child who should be on CAP.

There is significant heterogeneity in the patients selected and included in these several RCTs concerning CAP, so logically they will have differing outcomes. This may also be a factor in the ongoing NIH-sponsored RIVUR trial as well, but we must await those results. Even as we develop new data, it will be important to recognize that no single study can tell a clinician how to treat an individual patient. This is the so-called ecologial fallacy that the results of a study, no matter how well performed, will necessarily apply to an individual. It is incumbent on the clinician to determine how closely the patient in front of them fits with those in the study and if the recommended treatment approach is appropriate.

The role of BBD emerged as a critical and pervasive determinant of clinical outcomes in VUR. While there is need to improve defining, assessing or measuring BBD, its presence can generally be recognized and there are clinical strategies for treating it. It was seen to clearly influence the risk of further UTIs, likelihood of reflux resolution, and the outcomes of surgery. Therefore, assessing for BBD and including its presence in treatment choices were clear parts of the Guideline.

Active family participation in decision-making is integral to good care for VUR, as it reflects appropriate education and the recognition that parental preferences must be factored into the care plan. It also creates the foundation for appropriate long-term care that the pediatric specialist is unlikely to be able to provide.

A long-term follow-up plan is best implemented by the educated PCP in collaboration with the educated family. Reflux is a long-term health issue and the complications are seldom seen by the pediatric specialist, yet they can be very significant. If we forget how reflux first emerged into the medical consciousness in the 1950s and 1960s with hypertensive, azotemic young adults, these problems may recur, although the pediatric specialist is unlikely to see them directly.

It is with that recognition that the Guidelines have been framed, based on current data, as well as clinical judgment to hopefully meet the goals of reflux treatment to prevent acute infection, reduce the risk of renal injury and minimize the morbidity of evaluation and treatment. The Guidelines represent a future evolution of reflux care that will continue to change as we learn more about identifying those at risk so we may more specifically address our treatments to those who need them.
VUR Survivor Guide For The Pediatric Urologist
(Or, How the West Was Won)

Christopher S. Cooper M.D., FACS, FAAP
Professor and Vice Chairman of Urology, Director of Pediatric Urology, University of Iowa, Iowa City, IA

Current management of vesicoureteral reflux permits a glimpse of what life must have been like in America’s mythical old Wild West—a relatively lawless place where there were only a few accepted rules to govern one’s conduct. It was a time where innocent people sometimes got hurt and it could be difficult to know the good guys from the bad. I suspect most people tried to do the right thing by using their own common sense, undoubtedly influenced by their knowledge of how things had been done in the past.

For many decades the determination of who benefits from the diagnosis and treatment of vesicoureteral reflux has escaped pediatric urologists. The recent AUA guidelines derived by a group of respected experts following an extensive, systematic meta-analysis of the literature serve to confirm this fact. Remarkably, despite 2,028 articles being reviewed, the only ‘standards’ produced were that on initial presentation a child with VUR should undergo height, weight, and blood pressure measurement (serum creatinine if bilateral reflux), determination of symptoms of bowel and bladder dysfunction, family education regarding VUR, and, for those undergoing open or endoscopic operations, a follow-up renal ultrasound.

The rest of the AUA guidelines were recommendations or options that permit the physician a great deal of flexibility in the management of the child with VUR. For example, given a child with VUR over 1 year of age without bowel or bladder dysfunction, one management option may be antibiotic prophylaxis but another would be observation without antibiotics and another would be surgical intervention with either open or endoscopic methods. Welcome to Dodge City—the sheriff is gone!

The failure of the AUA committee to develop rigid standards was not a failure of the committee. The fact is solid data to determine what’s right and wrong regarding VUR has not been published. So, what are we—the pediatric urologists facing the relatively lawless world of VUR—supposed to do? I offer the following four steps to help manage patients with VUR.

The first step is to be humble and recognize what you/we don’t understand. In general, I believe much greater mistakes come from those who are over-confident than under-confident. Both groups may be ignorant, but the over-confident group is more likely to ignore data contradicting their actions or inactions. When it comes to reflux, no one has all the answers.

The second step is to use common sense and knowledge about the situation. There are a few things we do know to be true about VUR. Many children with VUR have renal scan abnormalities and the higher the grade of reflux the greater the chance of renal abnormality. Some of these are congenital (dysplasia) and some are acquired abnormalities (scars). The greater the renal abnormalities, the more likely a child is to develop hypertension and/or renal insufficiency.

VUR permits the transmission of urine from the bladder to the kidney. In the presence of a bladder infection bacteria may be transmitted to the kidney. A higher grade of reflux likely increases the chance of pyelonephritis by delivering a larger bacterial inoculum. The longer pyelonephritis remains untreated, the more likely permanent renal damage becomes (this fact demands the physician consider the social situation for any given patient). Many believe that the developing kidney in a younger child is more susceptible to injury.

In general, reflux itself is not as big of a risk factor for development of bladder infection as is bladder and bowel dysfunction. If I have a patient diagnosed with VUR after a UTI, I routinely tell the parents that the child has two problems. One is VUR, and the other is the risk factors that led to the UTI. We also know that dysfunctional elimination negatively affects reflux resolution rates and that treatment of bowel and bladder dysfunction decreases rates of UTI. Children with recurrent UTIs are at greater risk for subsequent UTI.

The third step is to treat each patient as an individual needing individualized attention. We must move past the obvious (i.e., age and grade of reflux) and gather additional information that will ultimately determine a tailored course of action.

Attempting to improve individualized patient management, we published several reports defining multiple factors predicting a child’s chance for spontaneous reflux resolution. One such factor independent of VUR grade is the instilled bladder volume at the onset of reflux during cystography. For example, a child over 2 years of age with Grade 2 reflux that begins only after filling the bladder more than 50% of his or her predicted capacity has a 1 and 2 year reflux resolution rate of 60 and 75%, respectively. However, if this same child’s reflux begins at less than 50% of the predicted bladder capacity, then the 1 and 2 year resolution rate drops to 7% at both time periods. Consequently, reporting of bladder volume at the onset of reflux should be demanded by pediatric urologists as standard practice for those performing VCGs or nuclear cystograms.

When considering management options for VUR, both the physician and parents benefit from an accurate assessment of the chance of spontaneous resolution. Various treatment options seem more or less reasonable based on this prediction, especially since many parents and physicians have concerns regarding many years of antibiotic prophylaxis. If a child is highly likely to resolve VUR within a year then operative intervention may be too aggressive. However, in the example noted above where the chance of reflux resolution in two years is only 7%, operative intervention may seem more reasonable.

Additional factors that impact the chance for spontaneous VUR resolution include gender, presence of dysfunctional voiding, history of UTIs, laterality and duplication, and renal abnormalities/scars. Trying to determine likelihood and timing of spontaneous reflux resolution in any given individual, taking into account all of these
variables, becomes extremely complex - beyond the capacity of simple Kaplan-Meyer curves. To this end, a user-friendly neural network computer model was created and is available for anyone’s use at www.urocomp.net. 15

This model incorporated variables previously evaluated by hazard regression to have prognostic impact. 13 In calculating a prediction for VUR resolution, the model adjusts the impact of each variable based on the presence or absence and value of the other variables. The figure demonstrates the user interface for this computer model. After entering an individual’s data in each field and pressing ‘Predict’ the computer predicts if the individual will resolve reflux or not within 2 years, also providing the odds ratio for this outcome. The accuracy of this model was subsequently validated in a group of Japanese children. 16 For patients who have had a renal scan, an updated computer model was generated incorporating this additional data to improve prognostic accuracy (ROC = 0.945) 17 and is available on the website.

Aside from an accurate estimate of a child’s chance for spontaneous resolution, an additional individual factor to be considered when providing tailored health care to a child with VUR is the social situation. A poor social situation may be one of the greatest, albeit least reported, risk factors with respect to the patient’s health and outcome. A child with VUR that is unlikely to receive prompt medical treatment for pyelonephritis is at increased risk for significant renal injury compared to one that receives prompt treatment. The former child may benefit from operative intervention in hopes of reducing the chance of renal injury from prolonged pyelonephritis.

The final step is to recall our goal is more than protecting kidneys - it is to provide excellent health care to protect the child, not only from UTI and reflux, but also from excessive studies and interventions. Accurate estimate of the likelihood for reflux resolution permits tailoring of the timing of follow-up studies or need for intervention. Assessment of the social situation leads to adjustments in follow-up and/or treatment. A strong family history of renal injury or failure to resolve reflux, or parental preference for prompt resolution, may also dictate early operative intervention. Although recommending quite different treatments for the “same condition” may seem counter-intuitive to what’s been done in the past, rarely do two children with VUR really have the “same condition.”

In summary, the neural network helps predict reflux resolution within 2 years, and the social history helps determine likelihood the family will comply with therapeutic recommendations. Together, these facilitate individualized management of VUR.

### Renal Damage Risk Assessment in Vesicoureteral Reflux

Akanksha Mehta, MD, Chief Resident in Urology, Division of Urology
Warren Alpert School of Medicine Brown University
Jason Machan, PhD, Assistant Professor, Departments of Orthopedics and Surgery
The Warren Alpert Medical School, Brown University
Anthony A. Caldamone MD Professor of Surgery (Urology) and Pediatrics, Division of Urology, Warren Alpert School of Medicine Brown University and Chief of Pediatric Urology Hasbro Children’s Hospital

The risk of renal damage due to vesicoureteral reflux (VUR) is variable. Most studies assessing risk have focused on the risk of persistence of VUR. However, renal damage, rather than persistence of VUR, is a more important determinant of VUR-related morbidity, and, therefore, a more clinically relevant end-point with respect to the decision for observation versus surgical intervention. We formulated a scoring system for the risk of renal damage from VUR, and then applied this system retrospectively to current patients with vesicoureteral reflux, to assess the degree to which pediatric urologists were following renal risk-based recommendations.

First we performed a literature review to accumulate evidence-based data focusing on the risk of renal damage associated with VUR. 15,16,22 A weighted scoring system was developed for the six risk factors identified: age at presentation, highest reflux grade, presenting complaint (febrile UTI, nonfebrile UTI, prenatal hydronephrosis), presence of DES, upper tract status, and breakthrough febrile UTI. The determination of DES was made based on clinical history alone. The status of the upper tracts was considered abnormal if dysplasia or scarring was noted on a renal ultrasound or DMSA scan. The overall score for each patient was then calculated by adding the scores for each individual risk factor.

This protocol was next applied to 220 randomly selected patients, pooled from ours and 8 other pediatric urology practices (Anthony Herndon, Christina Kim, Jean Hollowell, Lane Palmer, Jeffrey Palmer, Louis Wojcik, Aseem Shukla, and Richard Hurwitz), randomly selected on the basis of differential geographic distribution.

Each risk factor was tested as a predictor of surgical intervention in order to assess the degree to which these pediatric urologists had based their treatment decisions on these factors, using generalized estimating equations for binary outcomes.

Medical records of these patients were reviewed and the renal risk assessment scoring system applied. One hundred and eight patients

(continued on next page)
were managed non-operatively, while 112 patients underwent surgical intervention, either ureteral reimplantation or endoscopic injection. Results described below are summarized in the Table:

**Age at Presentation:**
Patients >4 years old at presentation were more likely to undergo surgical interventions than patients aged 1-4 years or those <1 year old.

**Highest Grade of Reflux:**
Although patients with grade IV-V VUR more often underwent surgical intervention than patients with grade I-III VUR, the difference was not statistically significant.

### Table: Chance of surgical intervention based on risk of renal damage

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Assigned Score</th>
<th>No. of Patients (%)</th>
<th>Frequency of Surgical Intervention</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 4 years</td>
<td>1</td>
<td>62 (28)</td>
<td>68%</td>
<td>68 vs. 39% (p=0.0034)</td>
</tr>
<tr>
<td>1-4 years</td>
<td>2</td>
<td>81 (37)</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>0-1 years</td>
<td>3</td>
<td>77 (35)</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td><strong>Type of UTI at Presentation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystitis</td>
<td>1</td>
<td>35 (16)</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>3</td>
<td>145 (66)</td>
<td>55%</td>
<td>No</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>40 (18)</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td><strong>Dysfunctional Elimination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary symptoms</td>
<td>2</td>
<td>25 (11)</td>
<td>72%</td>
<td></td>
</tr>
<tr>
<td>Urinary and bowel symptoms</td>
<td>3</td>
<td>28 (13)</td>
<td>54%</td>
<td>No</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>167 (76)</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td><strong>Status of Upper Tracts at Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral normal</td>
<td>3</td>
<td>171 (78)</td>
<td>45%</td>
<td>45 vs. 71% (p=0.0040)</td>
</tr>
<tr>
<td>Unilateral normal</td>
<td>2</td>
<td>44 (20)</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Bilateral abnormal</td>
<td>3</td>
<td>5 (2)</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td><strong>Breakthrough Pyelonephritis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>166 (76)</td>
<td>39%</td>
<td>39 vs. 97% (p=0.0009); 39 vs. 80% (p=0.0011)</td>
</tr>
<tr>
<td>1 episode</td>
<td>1</td>
<td>29 (13)</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>&gt;1 episode</td>
<td>3</td>
<td>25 (11)</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td><strong>Grade of Reflux</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I-II</td>
<td>1</td>
<td>64</td>
<td>42%</td>
<td>No</td>
</tr>
<tr>
<td>Grade III</td>
<td>2</td>
<td>97</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>Grade IV-V</td>
<td>3</td>
<td>59</td>
<td>64%</td>
<td></td>
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</table>
kidneys and unilaterally abnormal kidneys were compared. There were few patients with bilaterally abnormal kidneys.

**Breakthrough Febrile UTI:**

Patients with 1 or more breakthrough febrile UTIs underwent surgical intervention statistically more often than those without breakthrough infections.

**Overall Score:**

A positive relationship was noted between the overall score and the rates of surgical intervention, indicating the scoring system predicted practice patterns of the participating pediatric urologists (Figure).

Our data shows surgical intervention for VUR was statistically higher in children who were diagnosed >4 years of age relative to those <1 year of age, had renal dysplasia or scarring at the time of diagnosis of VUR relative to those with normal appearing upper tracts, and those with breakthrough febrile UTI.

Although increased reflux grade has been associated with increased risk for renal scarring, we found no significant difference in surgical rates based on reflux severity, indicating other factors (patient age, upper tract changes, breakthrough febrile UTI) outweighed perceived risk based on reflux grade alone.

Similarly, we found no difference in surgical rates for patients with DES versus without DES, which might indicate efficacy of therapy for the dysfunction elimination, and/or influence of breakthrough febrile UTI which may have occurred more often in these patients.

One limitation of our model is lack of multivariable regression analysis to more clearly define the relative relationship between factors influencing surgical intervention or not. The model also did not take into consideration any impact parental preferences may have played in decision-making. **Most importantly, while our model showed good correlation in recent practice patterns between pediatric urologists representing a geographic and age cross section, it does not indicate the actual risk posed by the selected factors for renal damage from VUR.**
The 2010 AUA VUR Guidelines recommend individualized risk-assessment in deciding options for reflux management. The principal objectives in the diagnosis and treatment of VUR are two-fold: to reduce febrile UTI recurrence and to diminish risk for renal scarring.

How many children with VUR treated for their first febrile UTI will have a second febrile UTI? Surprisingly few studies address this question, although the answer can be gleaned from patients with VUR enrolled in the no-treatment (or placebo) arms of several recent randomized controlled trials. Only a minority of patients had a 2nd febrile UTI, reported in 16-42% of patients during follow-up an average of 18-24 months. In addition, Penessi et al reported only 30% of VUR patients receiving no therapy had recurrent febrile UTI in 2 years, with 6% having 3 or more episodes within the first year and 2% during the second year. While recurrent febrile UTI despite bowel and bladder management is an indication for correction of VUR, few patients actually have that indication for intervention.

How many patients referred for urologic evaluation after febrile UTI have renal scarring? The 2010 VUR Guidelines Panel found data in only 4 studies to estimate that risk, and as the Panel was meeting, we decided in Dallas in 2008 to determine contemporary rates of renal scarring by obtaining DMSA renograms in all patients referred to us for febrile UTI and/or VUR.

Consecutive children referred between October 2008 and August 2010 with a history of VUR and/or febrile UTI underwent DMSA renography at least 3 months after acute UTI, if present. Data regarding gender, age, VUR grade, febrile versus nonfebrile UTI, and number of reported UTIs were entered in a prospectively maintained database. We recorded differential renal function and whether or not any focal renal defects (decreased uptake of radiotracer) were present on DMSA. Exclusion criteria included presumed congenital reflux nephropathy, defined as >20% ipsilateral function loss with no focal cortical defects, solitary kidney, ureteropelvic or ureterovesical junction obstruction, duplication anomalies with ectopic ureter or ureterocele, neurogenic bladder, and posterior urethral valves.

We chose 3 months (rather than 6 or 12 months) for DMSA renography based on practical considerations. First, patients commonly present to us approximately 4-6 weeks after febrile UTI having already had cystography, and a further delay beyond another 6 weeks for information regarding renal scarring decreases utility of that data for clinical decision-making. In addition, recurrent UTI will occur in some patients, the likelihood increasing over time, which further delays DMSA renography if the intent is to identify cortical defects.

Excluding 16 children with presumed congenital reflux nephropathy without focal scar, a total of 298 children were included: 243 (81.5%) female, average age 48.5 months (SD = 40.2; range = 3–213). Focal cortical defects on DMSA renography occurred in only 62 (20.8%) of the 298 patients.

Table 1 shows DMSA results according to the number of reported febrile UTIs. Note that 70% of patients with 3 or more febrile infections still had no evidence of renal scar. While likelihood for a positive DMSA scan increased with increasing number of infections, we do not know if DMSA changes occurred after the initial infection or subsequently.

Table 2 shows DMSA outcomes by grade of VUR, using the highest grade for those with mixed grades. Any grade of VUR increased the risk of focal defects on the DMSA scan versus no VUR, but there was not much clinical difference in scar rates among those without VUR compared to those with grades 1-3 VUR. Furthermore, over 50% of patients with grades 4 and 5 reflux had normal DMSA scans.

Multiple logistic regression was used to estimate the odds of abnormal DMSA, demonstrating the likelihood for focal DMSA defects increased with VUR, especially grades 4-5, febrile UTIs, and age (Table 3). Gender and nonfebrile UTIs did not increase the risk for focal renal defects.

The majority of children (79.2%) referred to our practice with VUR and/or a history of febrile UTIs did not have focal cortical defects on DMSA renography. As expected, focal renal defects occurred even in the absence of VUR. Among those with VUR, focal abnormalities occurred in less than 20% of patients with VUR grades 1-3, and only 50% of those with grades 4-5, suggesting the presence of other causal mechanism(s) besides VUR in the development of renal scarring that need to be defined.

What is the risk for developing new renal scarring among patients with a normal DMSA scan performed 3 months or later after febrile UTI? We are currently collecting that data in our patients, but an earlier study that repeated DMSA renography 2-10 years after negative DMSA scans in 355 patients reported only 5 patients (1.4%) had new focal defects despite known additional UTIs in approximately 30%.

Does the age of the child impact risk for renal damage? Despite widespread belief that renal scarring is more likely in younger children, our data show increased age was associated with a higher risk of abnormal DMSA. Others have reported age did not relate to likelihood for DMSA cortical defects, or that age older than 1 year correlated with abnormal DMSA. In one prospective observational study, only 7% of 72 term neonates with febrile UTI developed a renal scar on DMSA renography 6 months later. Similarly, we found focal DMSA defects in 5 (7.9%) of 63 patients less than 1 year, compared to 57 (24.3%) of 235 patients greater than 1 year. Accordingly, younger children presenting for evaluation after UTI and/or VUR cannot be assumed to have a greater likelihood for renal scar, and older children cannot be assumed to have a lower risk for renal scar.

It is possible that benefit from VUR therapy has not been demonstrated, in part, because the minority of patients theoretically most at risk for renal damage, i.e. those with renal cortical defects, had not been identified at diagnosis, with many studies (including some recent RCTs) focusing on the youngest cohorts of patients who appear less prone to renal scar.

Despite widespread belief that renal scarring is more likely in younger children, our data show increased age was associated with a higher risk of abnormal DMSA.
We began our study to establish prevalence of renal damage in children referred with febrile UTI and/or VUR, but our findings have strongly influenced daily clinical practice. If the minority of patients with cortical defects on DMSA scan at least 3 months after UTI represent a group at risk for additional damage with future infection, prompt intervention may prevent further scarring. Given that 6 randomized, controlled trials demonstrate antibiotic prophylaxis is less effective that previously thought in reducing subsequent febrile UTI,2-7 we now suggest these patients have endoscopic injection or reimplantation to correct their VUR - even for those with low grade VUR that previously we would have observed on antibiotic prophylaxis while awaiting spontaneous resolution.

Other patients without DMSA cortical defects appear to have minimal risk for renal damage, even with future infection. We now observe these patients without antibiotic prophylaxis or surgical interventions, regardless of predicted likelihood for spontaneous reflex resolution. We obtain a second DMSA scan if febrile UTI recurs, but otherwise follow these patients without additional imaging, meaning we are not doing annual cystograms as we did previously. Indications for intervention in these patients include newly positive DMSA (which has not happened to date) or recurrent febrile UTIs (which, as mentioned above, is quite uncommon). This protocol is readily accepted by parents who are relieved to learn that there is no apparent damage - in some cases despite multiple febrile UTIs and high grade reflux.

If the majority of patients with VUR have neither frequently recurrent febrile UTI nor renal damage, how important is routine cystography in children after UTI? Based on our data, we no longer recommend it. We suggest initial imaging in a child with febrile UTI should only involve ultrasonography to identify the few with obstructive uropathy. In a variation of the ‘top down” approach,29 a DMSA 3 months later (rather than acutely) identifies the subgroup of patients most at risk from additional UTIs, who then undergo VCUG. This algorithm would reduce VCUGs to approximately 20% of children with febrile UTI, and avoid the need for a second DMSA in those with an acutely positive scan.

A common criticism of routine DMSA renography is that it does not greatly influence management. We too previously considered DMSA findings akin to closing the barn door after the horse escaped, yet our decision to incorporate DMSA renography as described resulted in significant clinical practice changes. Another criticism is that DMSA offers little additional information in patients with normal ultrasounds. Currently we are reviewing our data comparing renal ultrasound to DMSA, and it is apparent that patients with normal ultrasounds can have renal scarring and/or diminished ipsilateral function. Another possible criticism of our data is that cortical defects found 3 months after infection might not represent renal scars, being either unresolved inflammation or congenital cortical anomalies. This is true, and so our data potentially overestimates the risk of renal scarring in children!

It is clear many factors influence risks for both UTI and renal scarring in children. As the paradigm for the detection and management of VUR evolves, we believe delayed DMSA renography offers the best current means to assess risk for renal damage in children with VUR.

<table>
<thead>
<tr>
<th># UTI</th>
<th>Normal DMSA (n=236)</th>
<th>+ Focal Defect (n=62)</th>
<th>Total (n=298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>47 (87%)</td>
<td>6 (11%)</td>
<td>53 (18%)</td>
</tr>
<tr>
<td>1</td>
<td>95 (83%)</td>
<td>19 (17%)</td>
<td>114 (38%)</td>
</tr>
<tr>
<td>2</td>
<td>34 (76%)</td>
<td>11 (24%)</td>
<td>45 (15%)</td>
</tr>
<tr>
<td>3 or more</td>
<td>60 (70%)</td>
<td>26 (30%)</td>
<td>86 (29%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VUR</th>
<th>Normal DMSA (n=236)</th>
<th>+ Focal Defect (n=62)</th>
<th>Total (n=298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>68 (86%)</td>
<td>11 (14%)</td>
<td>79 (26%)</td>
</tr>
<tr>
<td>I-II</td>
<td>76 (82%)</td>
<td>17 (18%)</td>
<td>93 (31%)</td>
</tr>
<tr>
<td>III</td>
<td>69 (84%)</td>
<td>13 (16%)</td>
<td>82 (28%)</td>
</tr>
<tr>
<td>IV-V</td>
<td>23 (52%)</td>
<td>21 (48%)</td>
<td>44 (15%)</td>
</tr>
</tbody>
</table>

Table 3: Adjusted odds ratios were estimated for each risk factor and abnormal DMSA, while controlling for the other risk factors, using multiple logistic regression.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>$\chi^2$ and (p value) for Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02</td>
<td>1.01 to 1.03</td>
<td>19.25 (&lt;.0001)</td>
</tr>
<tr>
<td>Gender</td>
<td>1.71</td>
<td>0.63 to 4.45</td>
<td>1.14 (.286)</td>
</tr>
<tr>
<td>VUR I-II</td>
<td>3.05</td>
<td>1.20 to 8.19</td>
<td>5.54 (.019)</td>
</tr>
<tr>
<td>VUR III</td>
<td>3.12</td>
<td>1.17 to 8.73</td>
<td>5.16 (.023)</td>
</tr>
<tr>
<td>VUR IV-V</td>
<td>17.42</td>
<td>6.24 to 53.02</td>
<td>32.57 (&lt;.0001)</td>
</tr>
<tr>
<td>Febrile UTI</td>
<td>1.62</td>
<td>1.17 to 2.27</td>
<td>8.63 (.003)</td>
</tr>
<tr>
<td>NonFebrile UTI</td>
<td>1.03</td>
<td>0.77 to 1.37</td>
<td>0.06 (.804)</td>
</tr>
</tbody>
</table>

OR = Odds Ratio; 95% CI = Profile Likelihood Confidence Interval for Odds Ratios; $\chi^2$ = Likelihood Ratio Chi-Square Statistic. VUR coded as binary indicators with “No VUR” as the reference group; Gender was a binary indicator with female as the reference group; Febrile and NonFebrile UTI (rank-order scale 0-3); patient age was continuously measured in months.
CONCLUSIONS

It was a huge departure from the traditional paradigm that all children with reflux need therapy for the 2010 VUR Guidelines Panel to list observation as an option in some cases. But our long-standing assumptions that reflux needs to be diagnosed after UTI, and that antibiotic prophylaxis diminishes likelihood for recurrent infection, were both challenged by RCTs conducted largely by non-urologists. Non-urologists most often diagnose and treat UTI, and then decide if imaging and referral to pediatric urologists are indicated. Our specialty must help verify that VUR is a modifiable health risk if we expect to continue managing children with the condition.

While this Dialogue attempts to define patients at greatest risk from reflux, it is clear we do not yet have the data needed to identify those most at risk, nor proved that identification and therapy of patients with perceived high risk changes outcomes. As pediatric urologists we are experts in correcting reflux, but novices in determining who benefits from our interventions.

For example, Dr Peters emphasizes the role of BBD in UTI development and VUR management, yet admits diagnosis and therapy for this condition remains ill-defined.

Dr Cooper assesses VUR risk largely by likelihood for VUR resolution, refining the 1997 Guidelines Kaplan Meyer curves with a computer model calculating additional factors besides VUR grade. Yet a recent analysis of 3 available computer models shows considerable variation in their predictions for given clinical scenarios. Furthermore, does it matter when, or if, reflux resolves if a child has few recurrent febrile UTIs and no renal damage?

Dr Bush (and I) propose risk assessment by “late” DMSA renography, but have no data that intervention after scarring prevents future additional scarring. Was the “big bang” theory correct that the initial infection results in most the renal damage that is likely to occur? If so, then our only justification for reflux diagnosis and treatment is to reduce recurrent febrile UTI in the small minority with frequently recurrent febrile UTIs. If not, if VUR therapy does prevent progressive renal damage in the minority of children prone to scarring, then management can be focused almost entirely on this subset comprising less than 20% of all those diagnosed with the condition.

Patrick Mohnihan once remarked we are all entitled to our own opinions, but not to our own facts. Based on the data reviewed in this Dialogue, it appears we will be diagnosing and treating fewer patients with VUR in the future that in the past. In this era of evidence-based medicine, our specialty should assume the lead in defining VUR risks and best treatment options.

Thanks to the contributors and to the Dialogues for this discussion on such an important topic!

REFERENCES