Randomized control trials are the ultimate level of evidence in determining appropriate management in medicine. As you will see in this Dialogues, each of the trials or guidelines that have been developed have done so with stringent science. As a result each will contribute in some way to our management of children with urinary tract infections and in particular with vesicoureteral reflux. None in and of itself will become the cookbook for management, however, but each will give us one more piece of the puzzle.

In interpreting any randomized control trial, one must be certain that the population that is studied indeed is reflective of the patient that you are taking care of. Some will fit but some will not. It is our job to recognize the differences and to apply the recommendations selectively. It is always a concern that the recommendations will be taken at face value and applied generically, which likely would not result in the best care for individual patients.
FROM THE GUEST EDITOR (continued from page one)

the investigation of antenatal hydronephrosis and/or sibling/family screening. Thus countless children underwent repeated VCUGs, prolonged CAP, and even surgery, because of the fear of potential scarring and end stage renal disease, despite never having had a single UTI! Hence the parallel to occult prostate cancer being diagnosed and treated without knowing the risk in that individual is obvious when it comes to VUR.

VUR and UTI are problematic. They are associated with the potential for making a child acutely ill, especially if they occur in tandem where VUR potentiates ascending infection. The IRSC demonstrated that although CAP and surgery are equally effective (or for that matter ineffective, depending on the side of the fence where one is sitting) if the outcome addressed is one of scarring. However, surgery has been demonstrated to be far more successful at reducing the risk of febrile UTI that is the acute illness. Since febrile UTI may be a “marker” of underlying uropathology, especially VUR, and knowing that UTI has a high likelihood of recurrence, then perhaps we should use this marker more rationally. Although no guidelines are perfect, and the AAP Guidelines have been criticized and have led to confusion amongst primary providers and tertiary specialists as well, many of the action points are relevant. Importantly, these guidelines pertain only to pre-potty trained infants and children beyond the newborn period that is ages 2-24 months. Thus there is no suggestion that they are to be extrapolated to newborns or older children. They strongly affirm that properly obtained urine specimen, with both the finding of a positive culture as well as urinalysis, are prerequisites to confirm a true febrile UTI. This may seem insignificant and self-explanatory, but in my prior 2 practices at least 50% of patients who had been referred for UTI evaluation and underwent VCUG had never had a urine culture, and many more never had significant fever. In speaking to numerous colleagues, this is not a unique experience amongst our specialty. The guidelines furthermore support shorter courses of appropriate oral or parenteral antibiotics. Thus proper identification of true patients with febrile UTI will clearly diminish “labeling” and inappropriate investigation and treatment of patients. Shorter course therapy, especially oral outpatient treatment, has obvious benefits of avoiding hospitalization, IVs and hence reducing costs. Moreover, the likelihood of overtreatment and hence selecting resistant organisms will also be reduced. I would hazard, therefore, that none of us disagree with these recommendations.

The problems with guidelines is that they are most applicable to a large group, rather than that unique single individual sitting in your office, the office of a tertiary subspecialist. In an era where one’s practice is being influenced by the interpretation of third party payers, and of course the legal system, the role of guidelines and how they are utilized, is called into question. Thus 2 points in the AAP Guidelines impact us may be contentious to say the least. These points are that CAP which is not useful in preventing recurrent febrile UTI and perhaps even more contentious, that routine VCUG is not indicated after 1st febrile UTI in face of a normal ultrasound in the age group studied.

The 6 controlled studies published in the literature between 2006-2010 examining CAP show that rates of symptomatic recurrent UTI are fairly similar, whether CAP is administered or not. Virtually all these studies (except the Swedish trials) investigated children with only mild-moderate VUR and none addressed BBD. The PRIVENT study, although showing that CAP is efficacious in preventing recurrent UTI in a large spectrum of patients, also reveals that 14 patients must be treated in order to prevent a single infection. In that study, scarring was not an end point and thus true pertinent renal sequelae are not measured and would require significantly longer follow up and a larger study population. This is really just not feasible. The Swedish study, although small in numbers investigated, demonstrated that in higher grades of VUR, both CAP and endoscopic correction were superior to surveillance in preventing UTI and new photopenic areas on nuclear scanning. Of importance in this study, which was in the same young age group that the AAP Guidelines address, VUR grades were III-V and females across the board were at risk of recurrent UTI and acquired renal changes, while males were spared. The AAP Guidelines do define some important risk criteria as well but fail to note the import of BBD, which is often present even in this young age group.

In a perfect world, we would have a scenario where all patients were compliant and understanding of diagnostic and therapeutic options and were monitored by uniformly up to date, competent primary providers. Like VUR, there is a spectrum in both of these 2 parameters that impact a factor not elucidated in any guideline, “clinical judgment”. Is an 18 month old who lives 5 hours away from “sophisticated” medical care and whose patients are marginally educated, really the same as an affluent, educated family and patient who comes to office with masses of information that they have collected from the internet? Is the family of a child with VUR of any grade, in which a family member has lost a kidney or required renal replacement, going to accept guidelines in an unbiased fashion in a manner similar to a family with a negative history? Thus the “art of medicine” that must be applied to any given patient, given so much diversity, is a factor that is lacking in most guidelines.

We don’t know the true significance of an acquired long term photopenic area on a DMSA scan, but our own inherent assumptions that the majority will lead to clinically significant problems, is as blind as our prior assumptions that all VUR leads to scarring. We suffer from lack of quality long-term data and observation and referral bias are obvious. At 10 year follow up, the IRSC identified 4/252 (1.6%) developed hypertension, and these were primarily those with high grade VUR (IV). The entry criteria into the study required a creatinine clearance of 70 mL/1.73 m2 and only 1 of 133 at 10 years fell below that mark. Another separate study by Wannerwstrom followed 57 children with radiographic scars and 51 matched children without scars, 16-26 years after UTI. The GFR was reduced in those with bilateral scars but not in those with unilateral scars when compared to controls. Regardless of scars or no scars, hypertension was equal in both groups. The RIVUR study may be useful in the short term to identify acquired renal changes in those receiving CAP vs. those monitored expectantly, but is it clear that even that study will lack the necessary long-term data that really defines the significance of a radiological finding only. Perhaps as a guest editor, I can invoke that honor and privilege by expressing my own closing opinion based on what we do know about VUR and UTI and my own 3 decades in transplantation. UTI and VUR
should not be viewed as having a likelihood of causing CKD, especially ESRD, unless the kidneys have developed abnormally in utero with inherent CKD being predeterminated rather than preventable. On the other hand, acute pyelonephritis is traumatic to child and parent and is an all too common, expensive occurrence in childhood, regardless of the fact that for the vast majority of these children, it is acute and reversible with largely “benign” sequelae. We do have substantial data that support the fact that we can reduce recurrent febrile UTI by intervening surgically and correcting VUR when it is a co-factor in such children. Moreover, over the past quarter century we have become very expert in dealing with concurrent issues such as BBD. Thus, we, as pediatric urologists, are uniquely qualified to interpret the guidelines and explain the myriad of options to each family and their child and apply them individually.

This issue of Dialogues was conceived well before the AAP Guidelines were published. I have asked Craig Peters to address antibiotic prophylaxis from a “neutral viewpoint.” Guy Hudson served on Craig’s panel for the AUA Guidelines on VUR, and as a “younger” member of the committee invited him to describe the process and impact that serving on that committee had on him. Watson, Rajimwale, Williams and Shenoy for the Midlands of England comment on the true impact of the NICE Guidelines, guidelines that are even more stringent in my opinion than those of the AAP, and relate the impact on nephrourological practice in their environment. Ulla Sillen, a long time student of VUR and UTI summarizes pertinent data from the Swedish study and Grahame Smith from Sydney then presents a thoughtful analysis on lessons learned from the PRIVENT study in comparison to the Swedish data. Lastly, Saul Greenfield presents his thoughts about the ongoing RIVUR study.

Antibiotic Prophylaxis for Reflux: Why and When I Won’t Use It

Sheikh Zayed Institute for Pediatric Surgical Innovation, Children’s National Medical Center, Washington, D.C.

While the universal use of continuous antibiotic prophylaxis (CAP) for vesicoureteral reflux (VUR) has been effectively challenged and it should no longer be used automatically, we must make a careful clinical decision when choosing to use or not to use this treatment approach. There are clear data that indicate an absence of benefit for CAP with VUR in the specific populations studied. There are also clear data from both modern and older studies that indicate a benefit to CAP in certain populations. Our task as clinicians is to accurately determine which population the patient sitting before us belongs to, and we have limited, but still useful tools to do this. The strategy I use in deciding when not to use CAP for demonstrated VUR continues to evolve. My choice reflects the goals of reflux treatment that should 1) prevent acute infection, 2) reduce renal scarring and 3) minimize the invasiveness of treatment and evaluation. It will generally take a more cautious approach based upon the inherent unpredictability of an acute episode of pyelonephritis with possible (but by no means certain) renal scarring in an individual. My approach also actively involves parental preferences which must be sought and included in the decision making process.

The ideal child with VUR who does not need CAP is the one who will not have another UTI that might cause scarring. While we cannot absolutely predict this, we can look for the contributors to UTI. Obviously anatomic abnormalities will add risk, as will voiding abnormalities. The presence of Bladder and Bowel Dysfunction (BBD) needs to be sought, and if there is evidence of its presence, CAP would be used. In its absence, the risk of UTI is much lower, as is the risk of VUR persistence. The child who has not had a long string of prior UTI’s is less likely to have another. The circumcised boy will have fewer UTI’s in infancy and a slightly lower risk (from an already low risk) after infancy. The risk of scarring is difficult to predict, but the absence of scarring in children who have had infection is a good indicator of an apparently lower risk of further scarring. Of course, the presence of scarring would raise concern about susceptibility of more injury. The age of the child is important as well. If the child is in the midst of toilet training, discontinuing CAP is rarely appropriate as many of these children are acting like dysfunctional voiders, albeit temporarily. Similarly the 8 year old who has not had infections and voids well is unlikely to benefit from CAP. The older child will be able to verbalize symptoms as well, and is at lower risk for the systemic complication of pyelonephritis if it should occur.

The grade of VUR may be a relevant factor but this is unresolved. Clearly lower grades of VUR have lower risks of persistence and renal outcomes. Montaigne said: “There are no answers, only questions”. In VUR, there is more than a single question for that patient in your office, and resultantly, there also might be more than one answer for each one.

BIBLIOGRAPHY

Antibiotic Prophylaxis for Reflux  (continued from previous page)

scarring, but there is no clear cutoff, and some children with grade IV VUR have been managed off antibiotics with good results. Higher grades will be more likely to persist and the issue of the long-term impact of the VUR in young adult-hood must be considered, but there are no data to support one approach or another. In my practice, it is difficult to leave ongoing VUR if it is greater than Grade III; others are comfortable with this however. Grade III and less is therefore one of the criteria for stopping CAP.

Identifying these risk factors is largely based on a good history and examination. The need for DMSA scanning must be based upon the perceived risk as well as the history of infection and grade of VUR. The most important element in my practice has been the determination of the existence of BBD. I approach most children with the assumption that they have BBD and attempt to rule it out. The history should focus on toilet habits that suggest voiding postponement. Children who do not void on awakening in the morning are likely holders. The presence of wetting, even if just dampness, is a strong indicator. Bowel habits are equally important and we attempt to gain a specific record of the number and character of bowel movements. The simplistic question “is your child constipated” is of little value. Most parents are not very aware and may assume normalcy because it is the family pattern. Of course a brief examination of the lower back and spine as well as the feet is useful to detect the rare case of an occult spinal dysraphism. A voiding diary may be needed to better ascertain actual voiding patterns and at times a urinary flow rate with a post-void residual measure is useful. In the absence of these factors, the risk of further UTI is low.

One will obviously ask if the risk of UTI is low enough to justify not using CAP. This becomes a subtle clinical judgment that must be made with a good assessment of the child’s situation and the family’s inclinations. The latter will often depend upon how they came to learn about the reflux; those who have seen an acutely ill child with pyelonephritis in hospital, will usually request the use of prophylaxis. The decision is often one that evolves with time, after a period of observation with CAP.

The child who will be unlikely to benefit from CAP for VUR is the one with low risk of UTI and scarring. The clinical scenario is the older child, after toilet training, who has no evidence of BBD, lower grades of VUR, no recent history of UTI’s and a normal renal ultrasound or DMSA scan. The parents should be willing to accept the responsibility and uncertainty of both the short term and long-term risks of such an approach. In the short term, if the child develops a UTI, it can make the decision-making straightforward as that demonstrates the need for CAP or curative intervention (particularly if the child is older). The long-term risks of ongoing but asymptomatic reflux as the child moves into young adult-hood are unknown, but the issue must be presented as part of the decision-making.

In making the choice of not using CAP one both simplifies VUR management and adds complexity. Simplification comes for the family in not needing to remember to give an antibiotic every day, which is a highly variable capability. The lack of compliance is a common and serious issue impacting the use of CAP. Concerns regarding the short and long-term issues of using an antibiotic are eliminated; this is a universal worry voiced by parents. If the choice is made to not actively treat the reflux, its presence is no longer clinically relevant and the need for VCUG is erased. Some parents wish to know the status and the testing can be offered, but if one truly believes in the safety of no CAP, the rationale for a follow-up VCUG is limited.

The complexity of not using CAP cannot be ignored and one must view this as active a treatment program similar to using CAP. Unfortunately the approach of not using CAP carries the risk of being perceived as indicating everything is fine. Not using CAP cannot in any way be seen as discharging the patient to have a “nice life”. Therefore when CAP is not to be used for VUR, we maintain an active management program in collaboration with the pediatrician or primary care provider. Critically important to this program are 1) education, 2) accessibility and 3) targeted follow-up. Education as to the signs and symptoms of UTI, the importance of healthy voiding habits, and the need for consultation if problems arise must be provided to the family and they should demonstrate their understanding. Equally important is to maintain accessibility to care should an issue arise. This is usually best with the PCP, but the specialty team must be an available back-up. Rapid diagnosis and treatment of an acute UTI is likely to limit the risk of scarring and may reduce the morbidity of the episode. The specialty team must be available to the PCP as well for guidance on the interpretation of urine cultures and clinical episodes. To ensure that this approach is being adhered to, targeted follow-up is important. This can be by the PCP or the specialist, but should focus on history of possible UTI’s, voiding habits, overall health, and an occasional renal ultrasound. The frequency should be determined by the severity of the reflux, age of the child and any concerns regarding occult infection. Annual blood pressure determinations are needed if only to provide a baseline for later.

The thoughtfully selected child with VUR who is not placed on CAP is likely to do as well if not better than some others with VUR, likely due to their lower risk. Not using CAP can never be an excuse for negligence, but can be an appropriate and preferable management in the right child. The child with limited risk of recurrent UTI and scarring who has normal voiding habits, even with ongoing VUR, is likely to do well in the long-term. This clinical strategy requires thorough family education, accessibility to care-givers and a clear follow-up plan. If carefully managed, it will be a significant benefit to many children with VUR.
Lessons from the Guidelines: Understanding Evidence-Based Vesicoureteral Reflux Treatment in 2010

The 2010 Vesicoureteral Guidelines published by the American Urologic Association Vesicoureteral Reflux Guideline Committee are vastly different from the 1997 version. In 2006 I was asked by Drs. Steven Skoog and Craig Peters to join the Vesicoureteral Reflux (VUR) committee. This opportunity came only one year into my career at Oregon Health and Science University where I had returned to practice after completing my fellowship with Dr. George Kaplan in San Diego, I welcomed the chance to make a contribution to one of our most common practice dilemmas. I began the project with fellowship-gained ‘expertise’ in the evaluation and treatment of VUR, but soon realized that we are far from evidence-based management of this condition.

The update contains only four standards and limited concrete statements. The 2010 Journal of Urology publication is the culmination of data review consisting of 2028 articles (1994-2008), of which 469 were reviewed in-depth. However, only 190 of those articles were used for the final analysis. Data organization was based on the answer to five clinical questions of common scenarios in VUR evaluation and management that we as practitioners face daily. The data represent 23,259 cases collated into a database for meta-analysis. After four years of countless teleconferences, in face-to-face meetings, discussions, and reviews, the project was finally completed.

Data analysis revealed our limited, fact-based knowledge of VUR and indicated most treatment is based on physician preference or bias. This is a direct result of the lack of appropriate randomized controlled studies in children with VUR—most studies in the literature are underpowered prospective randomized studies or retrospective. Flaws exist in our evidence-based understanding of VUR which precludes draft-powered prospective randomized studies or retrospective. Flaws exist in children with VUR—most studies in the literature are under-powered prospective randomized studies or retrospective. Flaws exist in our evidence-based understanding of VUR which precludes draft-powered prospective randomized studies or retrospective.

Continuous Antibiotic Prophylaxis

Continuous antibiotic prophylaxis (CAP) may not be needed to protect against urinary tract infection or scarring in all children. Antibiotic prophylaxis has been a mainstay of medical management for decades. Some children take antibiotics for years, with a presumed benefit of decreased risk of UTI, while waiting for the VUR to resolve. Repeated antibiotic treatment is commonplace even though few data support its use in all patients. However, antibiotics are not benign and their use should not be prescribed in a cavalier fashion. Several studies question the use of antibiotics in all patients with VUR as we are realizing that not all patients exhibit the same risk factors for the development of urinary tract infection and/or renal scarring. It is premature to completely abandon CAP for all children with VUR because some studies, such as the Swedish Reflux trial, show a benefit in select patients. Why do some studies show a benefit of CAP and others do not? The logical explanation is risk stratification. Although the data do not support the use of prophylaxis in all patients with VUR, it does not completely dismiss it either. Perhaps the RIVUR Study can assist in the answer to this question.

Bladder and Bowel Dysfunction (BBD)

The data show bladder and bowel dysfunction negatively impact VUR outcomes. VUR with BBD may be a genetically determined phenotype distinct from VUR without BBD. Refinement of the clinical definition, uniform assessment and treatment are essential to understand the full impact of BBD in this population. The data are clear regarding increased risk of UTI on CAP, decreased resolution rate of VUR, decreased success of endoscopic therapy, and a higher rate of post-operative UTI in patients with BBD. Perhaps more information can be gained in this population with genetic studies in order to under-

We should ask ourselves, is the main problem with VUR the morbidity associated with an increased risk of acute pyelonephritis or potential acquisition of renal scarring, the latter being in some cases of questionable significance?
Lessons from the Guidelines (continued from previous page)

stand the relationship between VUR and BBD. Particular focus on the clinical heterogeneity in relation to the inheritability of VUR may shed light on the impact of BBD and VUR as outcomes are clearly different in this population. It is likely that some children with VUR and BBD have secondary rather than primary VUR. If these children are incorporated into genetic studies and presumed to have primary reflux, identification of precise genetic markers is not possible. Therefore, identification of the genetic determinants of VUR will first need clear definition of the phenotype of interest. This identification will allow appropriate risk stratification for evaluation and management in these patients.

Future Endeavors

Future endeavors should include quality studies to clarify the issues surrounding VUR and development of logical, evidence-based management guidelines. Initial research efforts should focus on a few main points: development of reliable patient risk stratification models, national and international protocols regarding radiographic imaging techniques (the who and how of imaging), and genetic based studies for VUR.

In addition, the mechanisms differentiating developmental renal changes (congenital reflux nephropathy) and acquired renal injury related to acute pyelonephritis need to be understood for several reasons. Knowledge of the active mechanisms of renal injury associated with infection may permit more selective therapies as adjuncts to antibiotics. These areas of interest might include suppression or regulation of the inflammatory response, immune modulation, anti-fibrosis interventions, and cell death regulation. Understanding the patterns of response that may be distinct to certain groups would also permit identification of patients at greater or lesser risk of renal damage with infection, further supporting the goal of risk stratification of children with VUR. In addition, understanding the mechanisms of congenital reflux nephropathy may permit therapies to reduce the impact or progression of developmental renal abnormalities in post-natal life and may permit better prognosis of renal outcomes in those patients.

First, employment of risk stratification will allow identification of patients at risk for further pyelonephritis and potential renal injury. We realize in our practice that all children are different in regards to presentation, severity of illness, age, gender, ethnicity, family history, compliance, socioeconomic status, tolerances, genetic background and needs. All patients are not equal and therefore should not be treated the same.

Second, although the VCUG is the mainstay of diagnosis, the methods utilized in various academic centers varies widely. As the VCUG is an invasive study, the identification of the ‘at risk’ patient will help determine who will get this test. The current NICE Guidelines and the future publication of the AAP UTI Guidelines will help assist in this endeavor. Most of the RIVUR Study VCUGs are performed at referring institutions. Although they are scrupulously reviewed, consistency in the study performance is unlikely and difficult to ascertain. Reliable radiographic protocols will improve data collected in future studies.

Lastly, more studies to determine certain clinical aspects of APN in relation to the individual can predict future risk of renal damage or recurrent infection. Those determinants may include clinical response to infection, patterns of voiding behavior and demographics. All of these factors may have genetic factors at play which will influence clinical management.

Impact

Institution of the Guidelines in my clinical practice has evoked several changes. I no longer use long term antibiotic prophylaxis for most patients over a year of age. I am more consciously aware of the limitations of antibiotics and restrict their use. I do less imaging, ultrasounds and VCUGs, based on patient risk assessment for recurrent UTI. Bowel and bladder dysfunction patients are also managed differently than other patients with VUR in regards to antibiotic use, patient and family counseling, and operative intervention. The current confusion regarding global management stems from differences in acquired experience and the fact that an article supporting almost any treatment regimen can be found in the literature.

Conclusions

The 2010 Vesicoureteral Reflux Guideline provides guidance for evaluation and management of infants and children with VUR. It is not, nor is it intended to be, a standard of care in all patients with VUR. The document should be perceived as a roadmap, designed to alert us to several unanswered questions regarding the impact of VUR, especially in the setting of BBD.

Inherent deficiencies in the published literature were evident throughout the process. Strict criteria for design and publication of studies regarding VUR should be implemented

While this guideline, by design, did not address the question of which patients with UTI should undergo screening for VUR, this has become a critically important and controversial question. It relates directly to the issues of identification of patients at risk for further acute and long term health risks related to VUR and our ability to reduce this risk with therapy.

Although the VUR guideline provides some key observations and conclusions, investigators should respond to the inherent deficiencies in the literature. I am hopeful the next guideline will answer many questions surrounding the current controversies. In order to accomplish this, studies should begin now.

References

Critical Analysis of NICE Guidelines on UTI in Children: A Perspective from the UK

Ashok Rajimwale1, Alun Williams2, Manoj Shenoy2, Alan Watson3
1Paediatric Surgery, Leicester University Hospital, Leicester, England
2Paediatric Urology and 3Paediatric Nephrology, Nottingham University Hospitals, Nottingham, England

Introduction

Urinary tract infection (UTI) is one of the most common bacterial infections. The diagnosis of UTI is often difficult in young children as the presenting symptoms and signs are non-specific, and there are problems in collecting urine samples in young children (e.g. with bag, pad, clean catch specimen etc.)

The Royal College of Physicians of England (RCP) published an opinion-based consensus statement in 1991 on the diagnosis and the management of the first UTI in childhood. These guidelines advocated investigation of any child with proven UTI but there are problems as mentioned above. These investigations were intravenous urogram (IVU) and micturating cystourethrogram (MCUG) and subsequently refined to Ultrasound, MCUG and radionuclide imaging.

Since the publication of the RCP guidelines in 1991 it has been clear that the vast majority of children having an ultrasound (USS) and/or DMSA scan following a UTI have normal imaging. It is also felt the information obtained from the above investigations on preventable long term renal damage is relatively poor. Some investigations, notably MCUG, are unpleasant for children and distressing for their parents or carers. The current NICE (National Institute for Health and Clinical Excellence) guideline was published in an attempt to achieve more consistent clinical practice based on accurate diagnosis and effective management. In addition, in view of diagnostic uncertainty, the NICE UTI guidelines cross refer to guidelines on the investigation and management of the febrile child – namely that urine culture is needed when there is unexplained fever. NICE also attempts to make a distinction between ‘upper’ and ‘lower’ urinary tract infection.

UTI and its Importance

To reiterate, the classic signs and symptoms of UTI are usually lacking in very young children. The first UTI is most common in infants and affects boys more often in the first 3 months of life while the incidence of UTI in girls is equal to that of UTI in boys at 6 months of age. The incidence of first UTI falls with age in both sexes, however in boys up to the age of 6 months a UTI is more common. UTIs have been identified as major presenting features of underlying conditions such as vesicoureteric reflux (VUR), hydronephrosis or duplex kidneys. UTI has also been implicated as a factor causing kidney damage which can lead to end stage renal disease. It has also been found that infants who are treated for symptomatic urinary infections are at 26% risk of recurrent infection, usually in the first 3 months of follow up while in older girls the risk of recurrence following symptomatic urinary infection within 18 months, is approximately 60%. A study from the Goteborg childhood UTI research group found that children who have symptomatic or recurrent febrile UTIs, have a life-long risk of subsequent UTIs even in adulthood.

VUR and Voiding Dysfunction

It has been well documented in numerous reports that VUR is present in 35% of children with symptomatic documented UTIs. The incidence of VUR in children without UTI has been quoted at 0.4% – 1.8%. However a denominator is very difficult to quote given that

(continued on next page)
Critical Analysis of NICE Guidelines (continued from previous page)

Table: Recommended imaging schedule for infants younger than 6 months (Modified from Reference 3)

<table>
<thead>
<tr>
<th>Test</th>
<th>Responds well to treatment within 48 hours</th>
<th>Atypical UTI&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Recurrent UTI&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound during acute infection</td>
<td>No</td>
<td>Yes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Yes</td>
</tr>
<tr>
<td>Ultrasound within 6 weeks</td>
<td>Yes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>DMSA 4–6 months following acute infection</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MCUG</td>
<td>No</td>
<td>Yes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> See box 1 for definition  
<sup>b</sup> If abnormal consider MCUG  
<sup>c</sup> In an infant or child with a non-E. coli-UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks

Table: Recommended imaging schedule for infants and children 6 months or older but younger than 3 years

<table>
<thead>
<tr>
<th>Test</th>
<th>Responds well to treatment within 48 hours</th>
<th>Atypical UTI&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Recurrent UTI&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound during acute infection</td>
<td>No</td>
<td>Yes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Ultrasound within 6 weeks</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>DMSA 4–6 months following acute infection</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MCUG</td>
<td>No</td>
<td>No&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>b</sup> See box 1 for definition  
<sup>c</sup> While MCUG should not be performed routinely it should be considered if the following features are present:  
- dilatation on ultrasound  
- poor urine flow  
- non-E. coli-infection  
- family history of VUR.  
<sup>d</sup> In an infant or child with a non-E. coli-UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks

MCUG is required to demonstrate reflux, and incidence is, therefore, by definition subject to selection bias. It is known that the risk of both acute pyelonephritis and subsequent renal scarring is directly related to the severity of VUR. Under the age of 2 years, 36% of girls and 24% of boys, presented with UTI and amongst them 1/3 of girls and 2/3 of boys had dilating VUR.

It is acknowledged that VUR, which is often low grade resolves over time. The precise contribution of UTI and VUR to the development of end stage renal disease is difficult to ascertain, as it happens in many disparate groups in end stage programmes. Again it is acknowledged that renal dysplasia makes up the biggest diagnostic group in children coming to renal replacement treatment, and whilst VUR associates itself within this group of children, its implication in aetiology is far less clear.

The other important factor to take into consideration in older children is dysfunctional voiding. It has been found that 67% of girls with dysfunctional elimination syndrome (DES) develop UTI’s and 20% have VUR. Conversely 40% of girls with UTI have been found to have DES. In these children post pyelonephritic renal scarring was found to be more significant than anticipated for the grade of VUR present, which is secondary to the presence of residual urine and elevated voiding pressures. They have been found to be at a greater risk of progressive renal scarring estimated up to 44%.6,7

Renal Scarring

Renal parenchyma defects have been found in approximately 5% of children presenting with first time UTIs (boys and girls alike). The association and risk factors for acute pyelonephritis has been found to be associated with VUR, febrile and recurrent UTI’s and non E. coli infection. However, there is a tendency to overplay the association between UTI and scarring, particularly in counselling.

Hypertension

Less than 2% of the general paediatric population is hypertensive while a critical review in 1990 suggests that the rate of hypertension is 13% in children with a diagnosis of VUR over a follow up period of 18 months to 19 years. It has been found that the risk of developing hypertension in childhood is small and it is more common if the renal scarring is severe or bilateral. In adults who have a history of childhood UTI, between 5%-25% have diagnosed hypertension, therefore the development of renal hypertension may indicate a poor prognosis.3,9 Again, in counselling, there is a tendency to overplay the associations between UTI, scaring and hypertension.

Diagnosis of UTI, including Imaging

Difficulties in diagnosis have already been alluded to by the method of urine collection, and are reviewed extensively in the NICE guidelines. The imaging schedule is outlined in the table.

Pragmatically, prompt diagnosis and treatment of UTI, and the avoidance of ‘routine’ prophylaxis are the take-home messages of this section of the guidelines.

Implications for Clinical Practice of NICE guidelines

Unification of clinical practice by guidelines has had its proponents and dissenters.10 On the one hand, clear guidance ensures that a large number of children who would have had normal imaging are no longer subject to over investigation by unpleasant and traumatic tests2 which also lowers the burden of cost to healthcare providers. The recommendation of withholding ‘routine’ antibiotic prophylaxis also reduces the burden of giving medicine (and adherence to treatment) from families, and again lowers the cost burden.

The ‘twinning’ of the UTI and Febrile Child guidelines have clarified the need to consider UTI as a cause of febrile illness, and that prompt referral of young children can be important. A shift towards minimising investigations will avoid needlessly traumatic tests, unless UTIs are clearly atypical or recurrent, in which case the authors believe all such children should have the opportunity for early review.

On the other hand, healthcare professionals in the NHS face a changed philosophy in investigating and treating childhood UTI. It is (continued on next page)
Critical Analysis of NICE Guidelines (continued from previous page)

Table: Recommended imaging schedule for children 3 years or older

<table>
<thead>
<tr>
<th>Test</th>
<th>Responds well to treatment within 48 hours</th>
<th>Atypical UTI</th>
<th>Recurrent UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound during the acute infection</td>
<td>No</td>
<td>Yes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Ultrasound within 6 weeks</td>
<td>No</td>
<td>No</td>
<td>Yes&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>DMSA 4–6 months following the acute infection</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>MCUG</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

<sup>a</sup> See box 1 for definition

<sup>b</sup> Ultrasound in toilet-trained children should be performed with a full bladder with an estimate of bladder volume before and after micturition.

<sup>c</sup> In a child with a non-E. coli-UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks

Box 1: Definitions of atypical and recurrent UTI

<table>
<thead>
<tr>
<th>Atypical</th>
<th>Recurrent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seriously ill</td>
<td>Two or more UTI with acute pyelonephritis (‘upper tract’)</td>
</tr>
<tr>
<td>Poor urine flow</td>
<td>One ‘upper tract’ UTI / pyelonephritis + One or more UTI with cystitis (‘lower tract’)</td>
</tr>
<tr>
<td>Abdominal or bladder mass</td>
<td>Three or more ‘lower tract’ UTI</td>
</tr>
<tr>
<td>Raised creatinine</td>
<td></td>
</tr>
<tr>
<td>Septicaemic</td>
<td></td>
</tr>
<tr>
<td>Failure to respond to suitable antibiotic after 48 hours</td>
<td></td>
</tr>
<tr>
<td>Non E. coli</td>
<td></td>
</tr>
</tbody>
</table>

uncomfortable to regard the (small) number of children whose UTIs might have an underlying anatomical or functional abnormality. Yet a careful clinical history and physical examination including blood pressure measurement and urinalysis will uncover further risk factors that mandate investigation. This is implicit in that the NICE guidelines are aimed very clearly at physicians in primary care as well as those providing secondary or tertiary care.

Our own local studies (unpublished data) have shown substantial reduction in routine ultrasound and investigations compared with the 1991 guidelines for the same clinical relevant outcomes. It also showed further reductions in DMSA scans in our series where consultant radiologists perform the ultrasound and have shown comparable findings to DMSA. We would conclude that in centres who can achieve this standard on ultrasound, investigations can be limited further than the NICE guidelines. However, we would be cautious in recommending ultrasound alone in children younger than 6 months of age: studies would be needed to confirm that this is sufficient in this group of patients. We have found the multiprofessional approach involving nephrology, urology and radiology to be invaluable in rationalising the approach to investigation, and this is subject to ongoing local audit and review. Our own approach appears in the table.

Clearly the risk factor for UTI causing most anxiety, concern, and consternation to all interested parties is VUR. The treatment of VUR in itself has been controversial enough, and an optimum treatment paradigm is not resolved. The NICE guideline may restrict numbers in whom VUR is identified. Whether or not this has any bearing on the outcome (in terms of general health, UTI, or kidney function) of these children is another matter.

One big advantage of unifying practice by a guideline is that it gives us all an opportunity to audit a standard of management that will identify ‘missed’ children and allow modification of the guideline in due course if necessary. Our mission as a group who look after children with UTI is to identify those at risk of kidney (and urinary tract) damage and prevent its sequelae. Whether or not we have consensus before a guideline is a moot point.

References

Perspectives on BBD from the Swedish Reflux Study: Lessons Learned

Ulla Sillén, MD

Department of Pediatric Surgery/Urology Section, Queen Silvia Children’s Hospital, Goteberg, Sweden

In the Swedish reflux trial (SRT) in children (VUR grades III-IV, ages 1-2 years), prophylactic treatment, endoscopic injection and surveillance were compared in a randomised controlled study. The duration of the study was 2 years, and the primary endpoints new renal damage, recurrent UTI, reflux status and influence of bladder dysfunction. The children were investigated for lower urinary tract (LUT) dysfunction at the 2-year follow up at ages 3-4 years, using voiding history and flow/residual for diagnosis. Bladder function was also investigated at entry. At this age the children were not toilet trained and therefore the 4-hour voiding observation had to be used. The information from these latter studies (functional bladder capacity and residual urine) was not related to outcome of UTIs, VUR and renal damage during follow up and is not further discussed in this overview.

At the 2-year follow up, when the children were toilet trained, 34% of the VUR children were considered to have bladder dysfunction. Most (72%) had voiding phase problems, often including bowel symptoms (dysfunctional voiding (DV), dysfunctional elimination syndrome (DES)), while the remaining children were diagnosed as having isolated overactive bladder syndrome. No bladder treatment was given. The strength of the study from the LUT dysfunction point of view was the homogeneity of the material regarding both grade of reflux and age at all investigations, including investigation of renal function and reflux status. Furthermore, the data concerning recurrent UTI and type of infection (pyelonephritis or cystitis) were reliable. The drawback was that non-invasive investigations of bladder function were performed at a time when most of the children had just been toilet trained. Therefore, an increased number of voiding symptoms could be expected in comparison with what is seen in older children. It has not been scientifically determined whether voiding history as a diagnostic tool for bladder dysfunction is reliable in this age group.

In the following the results of the SRT are compared with data from the AUA guidelines for VUR. In these guidelines, background work has been done in an attempt to create scientific evidence for VUR management. From a large number of studies, those with the highest quality were chosen and included in meta-analyses of various aspects and results. It is important to point out that the SRT children are well defined both regarding age and VUR grade as mentioned above, whereas the AUA guidelines often include children of all ages and grades of VUR.

UTI

Children with VUR and LUTD had a higher prevalence of febrile UTI than those without LUT dysfunction in the SRT (33% vs 19%), which is in line with the meta-analysis performed in the AUA guidelines (44% vs 13%). The latter figures include children of all ages and all grades of VUR, which might explain the difference in frequency between the studies.

Resolution of VUR

LUT dysfunction is a negative prognostic factor for spontaneous resolution of reflux. This was obvious in the SRT (22% vs. 56% in LUTD and non-LUTD, respectively) and was also evident in the meta-analysis in the AUA guidelines (31% vs. 61%). However, in subgrouping the LUT dysfunction in the SRT, children with voiding phase dysfunc-

(continued on next page)
function results were taken from the 2-year follow up data. However, when children with high bladder capacity and residual urine at the entry investigation and/or LUT dysfunction at the 2-year follow up were included, new renal damage was significantly higher in the LUT dysfunction group (67% vs. 0%, p 0.037).

**Comments**

LUT dysfunction seems to influence the natural history of VUR relative to that of children without such dysfunction. Children with LUTD in combination with VUR, seem to be at higher risk of renal damage from presentation. It has not been conclusively shown whether LUT dysfunction is also a contributory factor for development of new renal damage. However, since UTI is more often seen in VUR children with LUTD, it should be expected that these children are at risk of new renal damage, owing to the known connection between febrile UTI and renal scarring. In addition, spontaneous resolution of VUR has conclusively been shown to be less when LUT dysfunction is present. There may also be a reduced success rate for endoscopic treatment of VUR in cases with simultaneous LUTD. All these findings suggest that bladder dysfunction negatively influences the natural history of children with VUR, and thus makes diagnosis and treatment of the dysfunction important, especially before antireflux procedures are performed.

**References**


---

**Perspectives on BBD (continued from previous page)**

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Swedish reflux Trial, %</th>
<th>AUA guidelines, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LUTD</td>
<td>Non-LUTD</td>
</tr>
<tr>
<td>UTI</td>
<td>33%</td>
<td>19%</td>
</tr>
<tr>
<td>VUR resolution</td>
<td>22%</td>
<td>56%</td>
</tr>
<tr>
<td>Success rate ET</td>
<td>62%*</td>
<td>90%</td>
</tr>
<tr>
<td>UTI after surgery (ET±open)</td>
<td>33%</td>
<td>12%</td>
</tr>
</tbody>
</table>

*Definition for success VUR ≤ grad 2
Lessons Learned from Recent Australian UTI Studies and a Comparison to Swedish Reflux Trial

Dr. Grahame Smith, MBBS
Department of Urology, The Sydney Childrens Hospital Network, Sydney, NSW, Australia

Introduction

Marty Koyle asked me to write some comments on the two recent trials I have been involved in. He wanted me to criticise the studies and be “my own worst critic”. Initially that sounded a good idea, but I was only one of many authors on the PRIVENT trial.1 That study was designed by Jonathan Craig, who is an expert clinical epidemiologist. So while there were compromises made to help recruitment, there were few problems that I could find in the study. The second paper that I was involved in was the paper describing a cohort of boys with high grade vesicoureteric reflux.2 This study was not designed with the same amount of thought and rigor and so I am able to comply with Marty’s request. Lastly, I couldn’t help but comment on the Swedish reflux trial.3 This was a most impressive trial, with a large amount of data produced and interesting findings. Such a significant study does warrant careful review and I acknowledge that it is easier to criticise such a study rather than to organise it and complete it.

The PRIVENT Study

At the end of the last century it was taught that prophylactic antibiotics should be given to children who were at risk of developing a urinary tract infections. This included children who were diagnosed with an abnormal urinary tract on an antenatal study, children who had vesicoureteric reflux, children who had had recurrent urinary tract infections and children who had dysfunctional voiding syndrome. The origins of the intervention were not altogether clear, but it had been become an established intervention. As the Cochrane methodology for assessing the risks and benefits of treatment developed, this methodology was used to look at antibiotic prophylaxis as an intervention in children at risk of urinary tract infection and to look at interventions for vesicoureteric reflux. When the evidence for prophylaxis was examined, it became apparent that there were no adequately powered, placebo controlled trials regarding its efficacy. The intervention began to be questioned and several trials were organised in various centres around the globe to examine the effectiveness of prophylactic antibiotics.

The PRIVENT study was designed to test the effectiveness of prophylactic antibiotics in preventing further urinary tract infections in children who had had one or more febrile urinary tract infections. Trimethoprim sulphamethoxazole was chosen as the study drug, since it was the standard therapy used as prophylaxis in our hospital, as well as being commonly used in other centres around the world. At the time of the study, trimethoprim suspension was not available in Australia. Further, the management of reflux was also being questioned and in particular the need to investigate all children after a single urinary tract infection. The need for a cystogram after a UTI was being questioned. For that reason, there were no imaging requirements mandated for participation in the trial.

It was difficult to recruit children to take part in the trial. Some physicians and some parents had very fixed ideas about whether or not children should have antibiotics. Some parents and physicians felt that the widespread use of antibiotics was leading to increasing bacterial resistance in the community and preferred to reserve antibiotics for treating actual infections. Some parents were concerned about the long-term use of antibiotics in children and the possible long-term adverse effects. Several were concerned their children would become resistant to antibiotics. Initially I thought this was confused thinking, but in a way they may turn out to be correct. Yet other physicians and surgeons felt that to not use antibiotics would pose a serious risk to the child, particularly in children who are known to have high-grade reflux. In order to improve recruitment, Microbiology Department data were used to identify all children with a positive urine culture and the patient’s parents were then contacted directly to offer them inclusion in the trial. It also became necessary to include other centres in the trial.

The study was conducted as a randomised, double-blind, placebo-controlled trial. Randomisation was performed at arms length an independent clinical trials Centre. It was stratified according to centre, referral source, frequency of previous urinary tract infections, reflux state, age and sex. The study was blinded, so the investigators and the treating physicians did not know which arm of the study the patients were in. There was an “at arms length” safety committee, monitoring the outcomes of the study. The study was funded by the NHMRC and ran from 1998 through to 2007. A total of 576 children were enrolled in the trial with a median age of 14 months. Seventy-one percent of the children were enrolled after their first urinary tract infection. There were 64% female is and 36% males. Forty two percent of the patients were known to have reflux. Four hundred and seventy seven (83%) patients had cystograms and 129 (22%) were known to have grade 3 or 4 reflux. The endpoint of the trial was either a urinary tract infection or 12 months of trial medication. For both entry and exit from the study a urinary tract infection was defined as a positive urine culture on a clean catch, in out catheter specimen or a suprapubic bladder. Bag urine results were not acceptable. The trial was analysed using an intention-to-treat analysis. There was a reduction in the incidence of urinary tract infections from 19% in the placebo group to 13% in the treatment group (P <= 0.02). So there was an absolute reduction of 6% in the incidence of UTIs. It was interesting to note that the difference in the incidence (continued on next page)
Lessons Learned from Recent Australian UTI Studies (continued from previous page)

of urinary tract infections was more in the first six months of the trial than in the second six months of the trial (see figure 1). Several other trials published during this period of time did not show any effect of prophylactic antibiotics, probably because they were not large enough trials to demonstrate this small effect.

Looking at prophylaxis in another way, combining both the risk of a UTI and the effect of prophylaxis, it turns out 15 children need to be treated for 12 months to prevent 1 UTI (figure 2). This population was chosen to be at high risk for a UTI, having already had 1 or more UTIs. So the number needed to treat would be even higher in a children who had never had a UTI.

Of the 576 children in the study, 468 underwent a DMSA scan. Thirty-one percent of the initial scans were abnormal and this was the same in both the treatment and the placebo groups. The great majority of the follow-up DMSA scans were either unchanged or improved. Seven percent of the DMSA scans in the antibiotic group and 8% of the scans in the placebo group looked worse. So omitting prophylaxis doesn’t seem to be a significant risk for progressive renal damage, when compared to observing children off prophylaxis.

Further subgroup analyses were performed looking at the effectiveness of prophylaxis in the different sexes, at different ages, with or without reflux with and with or without previous UTIs and whether or not the original infection had been resistant to trimethoprim sulphamethoxazole. When the children who had had an initial infection resistant to trimethoprim sulphamethoxazole were examined, it turned out that prophylaxis had very little effect. So perhaps the parents concerned about antibiotic resistance in their children were correct. One could speculate as to why this is so. Perhaps the child carried resistant organisms in their gut or perhaps the child was exposed to resistant organisms in their home environment. The study was not designed to test this observation and so it should be noted as an interesting observation, but one that requires further investigation.

As a result of this trial, it is reasonable to either give prophylaxis or not give prophylaxis according to the choice of the treating physician and the family. There is a small benefit, but not giving antibiotics does not result in a greatly increased risk of a urinary tract infection. As microbiologists voice their concern about the emergence bacteria that have multiple antibiotic resistance the pendulum may swing back away from the routine use of prophylaxis. The harm to the community may outweigh the small benefit to the patient.

High Grade Primary Vesicoureteral Reflux in Boys

We have also recently examined a cohort of boys with high-grade vesico ureteric reflux. In the same way that it was generally accepted that prophylaxis was indicated to prevent urinary tract infections, it is also in generally accepted that high-grade reflux needed to be treated because it placed the patients at significant risk of recurrent urinary tract infections and continuing renal injury. Both the Birmingham reflux study and International reflux trial did not show any clear superiority for surgical correction of reflux in preventing subsequently renal damage, although in the International reflux trial surgery to correct reflux did seem to reduce the risk of a febrile urinary tract infection by about half.

It seemed to us that the patients at highest risk of continuing renal injury would be boys with high-grade reflux. Scarring is seen more often in high-grade reflux. It is also more common with higher bladder pressures and boys void with a higher pressure than girls. Recurrent infections are also implicated in new scarring and boys have more infections in the first year of life, when kidneys are thought to be most susceptible to new injury. With a high likelihood of an adverse effect as a result of reflux, this seemed a good group to look at the benefits of interventions. Unlike the PRIVENT trial, this was an observational cohort study. The interventions were not randomised and it was not a blinded study.

There were 151 boys in the cohort. Fifty-two presented with an antenatal diagnosis of hydrenephrosis and were subsequently found to have grade 4 or 5 reflux. Ninety-nine presented after a urinary tract infection and were similarly found to have either grade 4 or grade 5 reflux. We excluded boys with secondary reflux, such as reflux secondary to a neurogenic bladders, bladder exstrophy, ureteroceles, posterior urethral valves or prune belly syndrome. DMSA scans were performed at the time of diagnosis, 12 months later, two years after that and then four years after that. Patients were maintained on prophylactic antibiotics until they were two years of age or until six months after diagnosis, if they were older than two years of age at the time they were diagnosed. Some boys underwent a circumcision and/or surgery to correct their reflux. Treatment was not randomised, it was based on the best advice at the time and on parental preference.

Renal defects were defined as baseline perfusion defects if they were seen on initial scan and as new perfusion defects if there were seen on 2 sequential follow-up scans. On the initial scan 41 of 52 (79%) boys in the antenatal group had defects and 74 of 99 (75%) boys in the UTI group had defects. This difference was not significant. This was a surprising finding. It would indicate that there is no urgency to diagnose boys with high-grade reflux before they have their first urinary tract infection, since there was no difference in the incidence of defects seen in the group who had had an infection when compared to the group who had never had a urinary tract infection. This data strongly suggests that the great majority of renal defects are present at the time of birth in this cohort. A single subsequent infection makes little difference to renal function.

Looking at the data on the follow-up DMSA scans, new permanent defects were uncommon with an incidence of 3.7 new permanent defects per hundred patients per year. A febrile urinary tract infection was documented in 72% of patients proceeding new defect formation. So these boys are not immune to new renal damage, it’s just uncommon.

Looking at interventions, the incidence of urinary tract infections before a circumcision or a ureteric reimplantation was about 45%. Af-
ter circumcision the incidence of UTIs fell to 7% and after antireflux surgery the incidence of UTIs fell to 18%. It is difficult to interpret this data, since urinary tract infections are more common in younger boys than in older boys (see figure 3). So whichever intervention is chosen, there will be a fall in the incidence of UTIs afterwards just because the boys are getting older. Since the median age at circumcision was 8.5 months and the median age at antireflux surgery was 30 months, I would have expected the antireflux surgery to seem more effective than circumcision. Older children should have fewer UTIs. Surprisingly, fewer UTIs were seen after circumcision than after antireflux surgery. The effectiveness of circumcision in preventing urinary tract infections in boys at high risk of infection clearly needs further investigation.

Again, surprisingly, the risk of a new perfusion defect in a normal kidney was similar to the risk in an abnormal kidney. The International reflux trial suggested that scarred kidneys were more likely to develop new damage than normal kidneys. We did not replicate this finding and our data would suggest that normal kidneys are just as likely to develop new defect as abnormal kidneys.

There were no adverse events seen following circumcision. Surprisingly, 3 of 28 boys who underwent ureteric reimplantation surgery developed significant complications with failure to empty their bladders in the post-operative period. It is difficult to know if this was due to a pre-existing bladder abnormality or if the surgery lead to impaired bladder emptying. The technique used was a standard Cohen cross trigonal reimplantation performed via the transvesical route.

Finally, we did see a relationship between dysfunctional voiding and both the incidence of UTIs and new perfusion defects. It was difficult to qualify, since it wasn’t easy to define a dysfunctional voider prior to toilet training.

The Swedish Reflux Trial

It is worth examining the recent Swedish reflux trial, to compare and contrast the results. The study included males and females and was a randomised trial comparing three management approaches. One group was observed off prophylaxis, one group was treated with prophylactic antibiotics and the third group was treated with Deflux. The study used DMSA scanning to follow children for new renal defects. Urinary tract infections included those diagnosed on a bag specimen, so that would tend to over diagnose the incidence of UTIs.

The data from this trial also showed that normal kidneys were just as likely to develop new renal defects as kidneys with baseline perfusion defects at presentation. If just the data from the boys were examined, then the study did not show any significant difference in outcomes between the three treatment groups. Girls were more likely to have problems with recurrent urinary tract infections and were more likely to develop new defects on DMSA scanning.

There were 128 girls and 75 boys in the study. The age range at recruitment was between 1 and 2 years, so beyond the age where boys are at highest risk for UTIs. The Swedish group also had difficulty recruiting patients. It would seem they have the same issue with clinicians and parents sometimes being wrong but never in doubt.

The investigators excluded children with grade 1 and 2 reflux, since they assumed this group was a low risk for UTIs and new renal injury. However, they did include the grade 3 VUR group and this group is at a significantly lower risk for renal defects at entry than the group with grade 4 reflux. The incidence of abnormal kidneys in the grade 3 refluxing group was 50% and the incidence of abnormal kidneys in the grade 4 refluxing group was 79%. So these are very different patient groups. Similarly, I note that grade 4 reflux resolves much more slowly than grade 3 reflux5 (figure 4).
I was interested to see that the authors reported a low incidence of new renal defects in boys. It didn’t matter how they were treated. So this finding agrees with our finding of a low incidence of new renal damage in the cohort study in boys with high-grade reflux.

Examining the data on the girls, there was a lower incidence of new renal defects if they were treated with either prophylactic antibiotics or with Deflux. In the first paper the authors state that “patients in the endoscopic group received prophylaxis until a new VCU showed absent VUR or improvement to grades 1 to 2.” It is not clear how long it took for Deflux treatment to be organised or how long it took for the postoperative VCUG to be organised. So the duration of prophylaxis therapy in the Deflux group is unclear and further the duration of dual therapy (both prophylaxis and Deflux) is unclear. This makes it difficult to assess the added benefit of Deflux treatment.

If the PRIVENT study data are taken as correct, then it can be assumed that prophylaxis has only a small effect in preventing urinary tract infection. Since new defects on DMSA scanning are associated with an increased incidence of urinary tract infections in almost all the reported series, it is surprising that the Swedish study demonstrated a reduced risk of new defects on DMSA scanning in the children in the prophylaxis group when compared to the control group. Perhaps prophylaxis somehow modifies the effect of a urinary tract infection and helps reduce the risk of a new perfusion defect developing, however, we did not see this effect in the PRIVENT study.

Lastly the fifth paper in the series is in my view the most important. The relationships between bladder dysfunction, infection and reflux were examined as was the responses to treatment. Renal damage at study entry and followup was more common in the children with lower urinary tract dysfunction (LUTD). Surprisingly, LUTD didn’t seem to predispose to UTIs. LUTD was associated with delayed reflux resolution and in particular children with voiding phase problems had delayed reflux resolution.

Future Areas for Research

It became apparent during a review of the literature for our study on boys with high-grade reflux that some authors contend that perfusion defects seen on a single DMSA scan can be separated into perfusion defects due to renal dysplasia and perfusion defects due to a recent urinary tract infection. It is generally accepted that some defects seen on DMSA scans after a febrile urinary tract infection will resolve on a subsequent DMSA scan. Presumably these defects are due to inflammation and/or oedema and are reversible. I remain unconvinced that defects seen on a single DMSA scan can be reliably classified as either due to renal dysplasia or due to a reversible lesion. So if our concern is to prevent further renal damage, then both a baseline DMSA scan and a follow-up DMSA scan are required to monitor for new renal injury. In my view, the sooner this occurs after diagnosis the better. It makes little sense to wait for 3 months for acute defects to settle. The children at highest risk may well have a further UTI during that period of waiting. Since it is now apparent that even normal kidneys can develop new perfusion defects, it seems worthwhile following all children at risk for new renal injury with serial DMSA scans. This is going to be the only way to determine who is at high risk for new renal injury and who is not. It is also the only way to see what treatments are effective in preventing renal injury. I had assumed boys with high grade VUR would be at highest risk of new renal injury, but it looks like girls with high grade VUR and recurrent UTIs are at the highest risk.

It has been standard teaching that annual cystograms are required to monitor children for resolution of their reflux. Cystograms are an unpleasant experience for children, particularly after toilet training. It may turn out that reflux by itself is not a risk factor for progressive renal scarring and if this is so then regular cystograms are not required in the absence of symptomatic UTIs and in the presence of a DMSA scan that has not changed.

It is also interesting to speculate as to why reflux resolves over time. I was taught that reflux resolves as the valve at the vesicoureteric junction matures and lengths. There is no data I can find to support up this theory. Attempts to look at orifice configuration and/or measure the sub mucosal tunnel length have not show a good correlation with reflux resolution. It seems more likely to me that reflux resolves as bladder function matures and bladder pressure drops with increasing age.

The final question that I would like to leave you with is “is there any such thing as primary vesicoureteric reflux?” In other words, are there really a group of children who have normal bladder function but who have reflux due to a deficient vesicoureteric valve? I have begun to suspect the answer to this question is no. I suspect all reflux is secondary to some degree of abnormal bladder function. I also think it is unlikely that reflux causes abnormal bladder function. It is much more likely that abnormal bladder function causes the reflux. I note with interest the recent paper in the Journal of Urology looking at the effect of alpha blockers on the resolution of reflux.

Since it is now apparent that even normal kidneys can develop new perfusion defects, it seems worthwhile following all children at risk for new renal injury with serial DMSA scans. This is going to be the only way to determine who is at high risk for new renal injury and who is not. It is also the only way to see what treatments are effective in preventing renal injury. I had assumed boys with high grade VUR would be at highest risk of new renal injury, but it looks like girls with high grade VUR and recurrent UTIs are at the highest risk.

It has been standard teaching that annual cystograms are required to monitor children for resolution of their reflux. Cystograms are an unpleasant experience for children, particularly after toilet training. It may turn out that reflux by itself is not a risk factor for progressive renal scarring and if this is so then regular cystograms are not required in the absence of symptomatic UTIs and in the presence of a DMSA scan that has not changed.

It is also interesting to speculate as to why reflux resolves over time. I was taught that reflux resolves as the valve at the vesicoureteric junction matures and lengths. There is no data I can find to support up this theory. Attempts to look at orifice configuration and/or measure the sub mucosal tunnel length have not show a good correlation with reflux resolution. It seems more likely to me that reflux resolves as bladder function matures and bladder pressure drops with increasing age.

The final question that I would like to leave you with is “is there any such thing as primary vesicoureteric reflux?” In other words, are there really a group of children who have normal bladder function but who have reflux due to a deficient vesicoureteric valve? I have begun to suspect the answer to this question is no. I suspect all reflux is secondary to some degree of abnormal bladder function. I also think it is unlikely that reflux causes abnormal bladder function. It is much more likely that abnormal bladder function causes the reflux. I note with interest the recent paper in the Journal of Urology looking at the effect of alpha blockers on the resolution of reflux.

References
The RIVUR Study: Crossing a Bridge

As discussed elsewhere in this issue of the “Dialogues,” the AUA guidelines are the most recent comprehensive attempt to make sense of the literature regarding urinary tract infection (UTI) and vesicoureteral reflux (VUR) in children. To the credit of the guidelines committee, they concluded that definitive recommendations for most clinical scenarios are not possible, given the many shortcomings of both retrospective and prospective studies. Meta-analysis techniques, as employed by the guidelines committee, cannot overcome these shortcomings. The Cochrane group similarly concluded that the literature is weak and that properly conducted, randomized and controlled clinical trials would be needed to provide statistically relevant therapeutic treatment recommendations. The RIVUR trial (Randomized Intervention for children with VesicoUreteral Reflux) is an NIH/NIDDK sponsored effort to conduct such a trial. It is the first of its kind in the United States and may be the last. It is an enormous effort, begun in 2005 and the results will not be known until after the trial closes in 2013. Aside from challenges of expense and the need for cooperation amongst multiple institutions, the prevailing attitude toward UTI and VUR in the pediatric community may make further studies of this nature impossible. Much hope rests, therefore, on the outcome of this trial.

Before describing the RIVUR trial, I would like to enumerate some of the most prominent faults in the existing literature: UTI is variously defined—bagged specimens are accepted from non-toilet trained infants, resulting in many false positives. Urinalysis data is also not always provided for each infection. Renal scarring is not properly assessed, either because upper tract imaging is not performed at all or because renal ultrasound, not radionuclide scanning is employed. Ultrasound is an unacceptable means of assessing renal scarring. Non-circumcised male infants are included in some studies and not in others. They have a higher incidence of UTI, with or without reflux, and so results from cohorts with large number of non-circumcised boys may not be generalizable to all children—circumcised boys or girls. Many of the large studies of children with UTI do not provide for complete radiographic evaluation of the urinary tract—so children with and without VUR and other hydronephrotic conditions are jumbled together, without identification. Voiding dysfunction in older, toilet trained children is poorly characterized, despite the fact that established tools are available to assess for dysfunction. When antibiotic prophylactic regimens are used, compliance with prophylaxis is not assessed. Most studies do not provide for blinded independent review of the voiding cystourethrogram (VCUG) to determine reflux grade or the dimercaptosuccinic acid renal scans (DMSA) to evaluate renal involvement. None provide 2 separate radiological readings to corroborate the findings. Some studies include older adolescents, who are known to be less susceptible to recurrent UTI and renal scarring. Finally, the numbers of subjects in other trials are often too small to yield statistically relevant results.

The entrance criteria and comparative arms for the RIVUR trial were the subject of exhaustive debate. This debate included clinicians—urologists, pediatricians and nephrologists—and epidemiologists. Factors which had to be balanced included—the need to answer the most relevant clinical questions; the ability to enroll the number of subjects needed over a limited enrollment period and clinical “equipoise,” so that risk to all subjects was minimized. Ultimately the protocol had to be approved by an impartial and supervisory Data Safety Monitoring Board (DSMB), who are also tasked with reviewing the unblinded data periodically. The DSMB has the authority to stop the trial if the data suggests that safety is compromised. The trial was supposed to finish in 2010, but due to delays in protocol development and challenges in subject recruitment it was extended to 2013.

The RIVUR trial is a 2-armed randomized, double blind and controlled study of 600 children comparing TMP/SMZ to placebo who are observed for 2 years. Boys and girls, ages 2 to 72 months with grades 1 to 4 VUR are included, who have had one or two prior UTI’s. Circumcision status is noted, although it is assumed that most boys in this cohort will be circumcised. VCUGs are obtained at entry and exit. There is an initial renal USG. DMSA renal scans are obtained at entry, at 1 year and at exit. All radiological studies are read by 2 independent radiologists, who enter their preliminary findings on line. Any differences are then adjudicated and a final reading is entered into the data base. Toileting function is assessed by validated questionnaire once they are toilet trained. Only catheterized urine specimens are accepted from non-toilet trained infants and all positive cultures must be accompanied by a confirmatory urinalysis. Medication compliance is enforced by every 2 month telephone contact and by monitoring medication refills and bottle weights every 6 months. Any clinical event, such as fever, pediatrician or emergency room visit, is carefully followed. Children are considered a treatment failure and removed from study medication if there are 2 febrile UTI’s, 4 non-febrile UTI’s, new scarring seen on a DMSA scan or parents want a change in treatment. Since this is an “intention to treat” trial, subjects off of study medication are still followed for the full 24 months. Study endpoints are the recurrence of UTI and the development of renal scarring.

At present, over 550 children have enrolled and so it is hoped that the recruitment goal will be met. It is already the largest study of its kind.
role of surgery—endoscopic, laparoscopic or open—will not be defined by this study.

As mentioned above, current attitudes in the pediatric community may make additional VUR trials difficult. Based upon data from poorly performed studies in this country and abroad, many pediatricians are not evaluating children after UTI with a VCUG, unless the infections are numerous or there is associated sepsis. The RIVUR trial may add credible data to either justify or condemn this practice. It is now also understood that the development of UTI—with or without renal involvement—may be due to a large number of risk factors, VUR being only one of them. Ultimately, we must acknowledge that there will not be a statistically valid study to answer every clinical question. The RIVUR trial is a model study and should be the basis for all contemplated clinical trials in pediatric urology. There is no doubt, however, that in many instances urologists will still have to individualize therapeutic recommendations without explicit guidance from a definitive trial.

References