Topic 1 - Management of vesicoureteral reflux in the child over one year of age

Contents

Index patient

The 4-year old patient with vesicoureteral reflux (VUR) and no clinical evidence of bladder/bowel dysfunction (BBD) who has presented initially with a febrile urinary tract infection (UTI) and a subsequent diagnosis of VUR by cystography.

Introduction

The association between VUR and febrile UTI was established in the 1997 AUA Guideline for Pediatric Vesicoureteral Reflux[1] based upon a significantly higher incidence of febrile UTI in children with ongoing VUR than in those with resolved or surgically treated VUR. Identification and management of VUR provides the potential opportunity to prevent renal damage. Children with UTI in the setting of VUR are at an increased risk for febrile UTI and pyelonephritis. Pyelonephritic episodes can be associated with renal scarring. The odds of renal scarring in children with VUR and pyelonephritis are 2.8 times greater than the odds of scarring for children with pyelonephritis without VUR. In order to reduce the morbidity of acute pyelonephritis and the risk of permanent renal injury, treatment of VUR is recommended. Treatment options include observation, continuous antibiotic prophylaxis (CAP), and interventions of curative intent.

Methodology

Literature Search, Data Extraction, and Evidence Combination

A meta-analysis of the existing literature was performed to define the outcomes of nonoperative and surgical management of VUR among toilet-trained children without evidence of BBD. The analysis defined 19 specific questions upon which clinical decisions are based. The questions were grouped into three categories; 1) those evaluating the causal relationship between VUR, pyelonephritis and renal injury (no causal relationship can be established with the design used in the majority of studies), 2) those determining the outcomes following treatment with CAP and 3) the outcomes of therapy with curative intent (endoscopic and open surgical intervention).

In all, 205 articles were evaluable, and data from 84 studies reported from 1994 to 2008 were extracted and meta-analyzed. Some studies included children younger than one year and outcomes were not separable for younger and older children. Also, some evidence may include non-toilet trained children (>1 yr of age). Data were extracted on 11,837 children: 578 children who underwent observation in seven studies, 3,311 children who received CAP in 29 studies, 4,587 children who had open surgery in 33 studies, 626 children who received macroplastique injection therapy in 7 studies, and 2,735 children who received dextranomer/hyaluronic acid injection therapy in 17 studies.

In addition, a subanalysis was conducted to determine the possible association between acute pyelonephritis, VUR and renal scarring. A meta-analysis was performed comparing

the incidence of renal scarring after the occurrence of an episode of acute pyelonephritis in children with VUR to those without VUR. The articles for the subanalysis, which were not selected in the initial literature review, included only studies in which children had acute pyelonephritis based on technetium-99m-labeled dimercaptosuccinic acid (DMSA) abnormalities and who were re-evaluated by DMSA more than 6 months after the acute event. These studies were not exclusively comprised of children with VUR. The remaining criteria used in selecting articles for this subanalyis are described in the methodology. Any study not meeting these strict criteria was excluded. Included in the analysis were eight studies of cohorts assessed between 1992 and 2006, with five (63%) studies being prospective. In all, at least 266 children with VUR and 444 without VUR were examined with a second DMSA for the development of scarring.

A summary of outcomes of the meta-analysis and relevant Guideline statements for management of VUR in the child over 1 year of age is presented below.
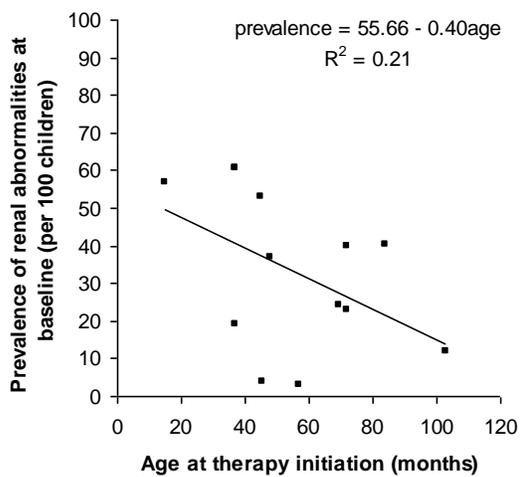
Initial evaluation of the Child with VUR
VUR, Acute Pyelonephritis and Renal Injury

The first set of questions assessed the association between VUR and renal injury using DMSA abnormalities, somatic growth impairment, hypertension, and renal insufficiency as indicators. Correlation of DMSA abnormality with age at diagnosis and reflux grade was evaluated; since most studies did not specify the age at diagnosis, the age at initiation of antibiotic or surgical therapy was used as a surrogate. The prevalence of renal cortical abnormalities decreased by 5.5% per yearly increase in average age at initiation of
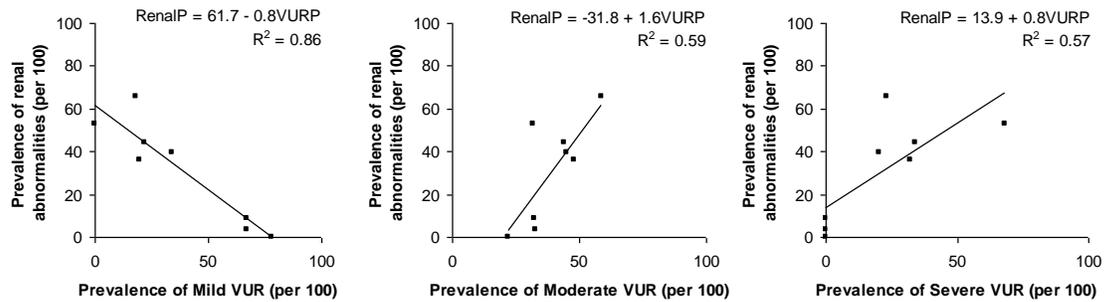
therapy (Figure 1). In studies with younger patients, the prevalence of DMSA

abnormalities was higher than in studies with older children. It is unclear if this reflects a

selection effect or demonstrates a greater tendency for DMSA abnormalities in younger

children.

Figure 1. **Relationship between renal cortical abnormalities on DMSA scanning and age at initiation of therapy**

Although few studies explicitly described DMSA abnormalities by VUR severity, studies

with a greater proportion of children having VUR grades I-II demonstrated a lower

prevalence of renal cortical abnormalities, while a higher prevalence of renal cortical

abnormalities was seen in studies of children with grades III to V VUR (Figure 2).

Figure 2. Prevalence of renal cortical abnormalities by VUR severity (by patient)

The number of studies using somatic growth, hypertension, and renal functional loss as indicators were limited. The evaluation of somatic growth impairment was assessed in one study with 94 children diagnosed with VUR following a UTI.[2] Children with bilateral reflux and scarring were more likely to have baseline growth impairment, starting with a height Z score of -0.45, in contrast to +0.18 in those with unilateral reflux and scarring. With either medical therapy (CAP) or surgical therapy, clear catch-up growth was demonstrated in those with bilateral reflux and scarring, with a height Z score of +0.21 after a mean of 3.1 years.[3] In nine studies reporting data on hypertension, the incidence was 1 per 100 children (95% confidence interval [CI]: 0.4, 2.8). These studies were limited by a short duration of follow-up in most cases. The few studies with long-term follow-up[4] suggest there is an increased incidence of hypertension over the long-term and it would seem prudent to recommend monitoring blood pressure at routine follow-up visits in children with known VUR and certainly in those with renal scarring.[4] Similarly, the incidence of renal insufficiency in eight studies was determined to be 1.7 per 100 children followed (95% CI: 0.3, 8.2). It should be noted that definitions of functional
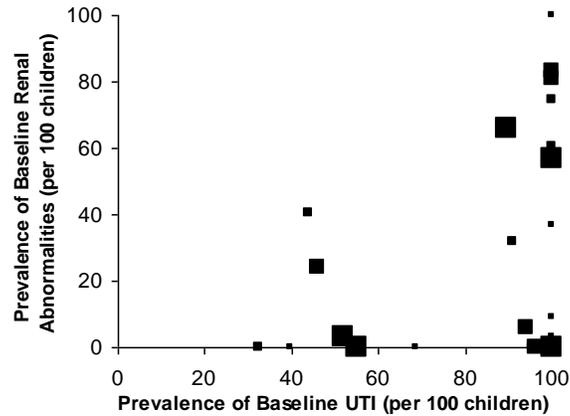
renal loss were variable and included decreased differential function of more than 6% on radionuclide imaging, elevated serum creatinine, renal failure, and end-stage renal disease.

Association between Renal Damage and UTI

To determine whether there was an association between renal damage and UTI, three approaches were used: 1) evaluation of whether the incidence of renal damage was greater for those presenting with UTI versus those not presenting with a UTI; 2) evaluation of whether the number of prior UTIs was related to the incidence of renal injury (this could not be addressed due to a limited number of studies); and 3) evaluation of the outcomes of studies in which the incidence of new renal cortical abnormalities occurring more than 6 months after an episode of strictly defined acute pyelonephritis were correlated with the presence or absence of VUR.
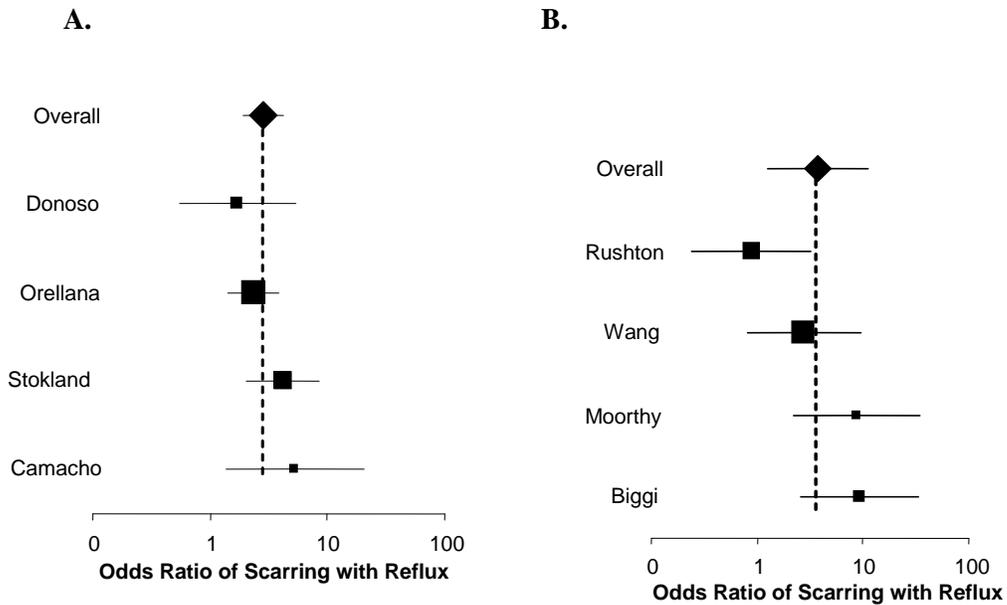
Although the relationship between the initial incidence of UTI and the presence of DMSA renal cortical abnormalities in the setting of VUR may reflect the interplay of multiple factors, a higher prevalence of baseline UTI appeared to be associated with a higher prevalence of renal cortical abnormalities (Figure 3).

Figure 3. Relationship between baseline UTI and DMSA renal cortical abnormalities

To determine whether children with VUR are at greater risk of having permanent renal injury following acute pyelonephritis compared to those without VUR, the incidence of both acute and permanent DMSA cortical abnormalities in children with and without VUR were analyzed. A 2.8 fold increase in the risk of permanent DMSA cortical abnormalities in the children with VUR and a 3.7 fold higher risk for individual renal units were found (Figure 4), showing that VUR is a significant risk factor in the development of acute pyelonephritis and subsequent renal damage in children.

Figure 4. Forest plots of odds ratios on a log scale of scarring after acute pyelonephritis among children with VUR compared to those without VUR. A) by patient; B) by renal unit.

Standard: VUR and urinary tract infections may detrimentally affect the overall health and renal function in affected children. Therefore, on initial presentation the child with VUR should undergo a careful general medical evaluation including measurement of height, weight, and blood pressure, and serum creatinine if bilateral renal abnormalities are found.

[Based on Panel consensus]

Recommendation: Urinalysis for proteinuria and bacteriuria. If the urinalysis indicates infection, a urine culture and sensitivity is recommended.

[Based on Panel consensus]

Recommendation: Because VUR and urinary tract infection may affect renal structure and function, performing renal ultrasound to assess the upper urinary tract is recommended.

[Based on Panel consensus]

Option: A baseline serum creatinine may be obtained to establish an estimate of glomerular filtration rate (GFR) for future reference.

[Based on Panel consensus]

Option: DMSA (technetium-99m-labeled dimercaptosuccinic acid) renal imaging can be obtained to assess the status of the kidneys for scarring and function.

[Based on review of the data and Panel Consensus]

Continuous Antibiotic Prophylaxis in the Treatment of VUR

Current standard therapy for VUR includes the use of CAP to prevent acute infection with the anticipation that spontaneous resolution of VUR will occur in a significant proportion of children.[1] Outcomes of treatment with CAP were evaluated in terms of incidence and character (cystitis, febrile, nonspecified) of UTI, incidence of new renal cortical abnormalities and the resolution of VUR.

UTI Incidence

Results of analysis of the incidence of UTI in children receiving or not receiving CAP in 18 studies are presented in Table 1.
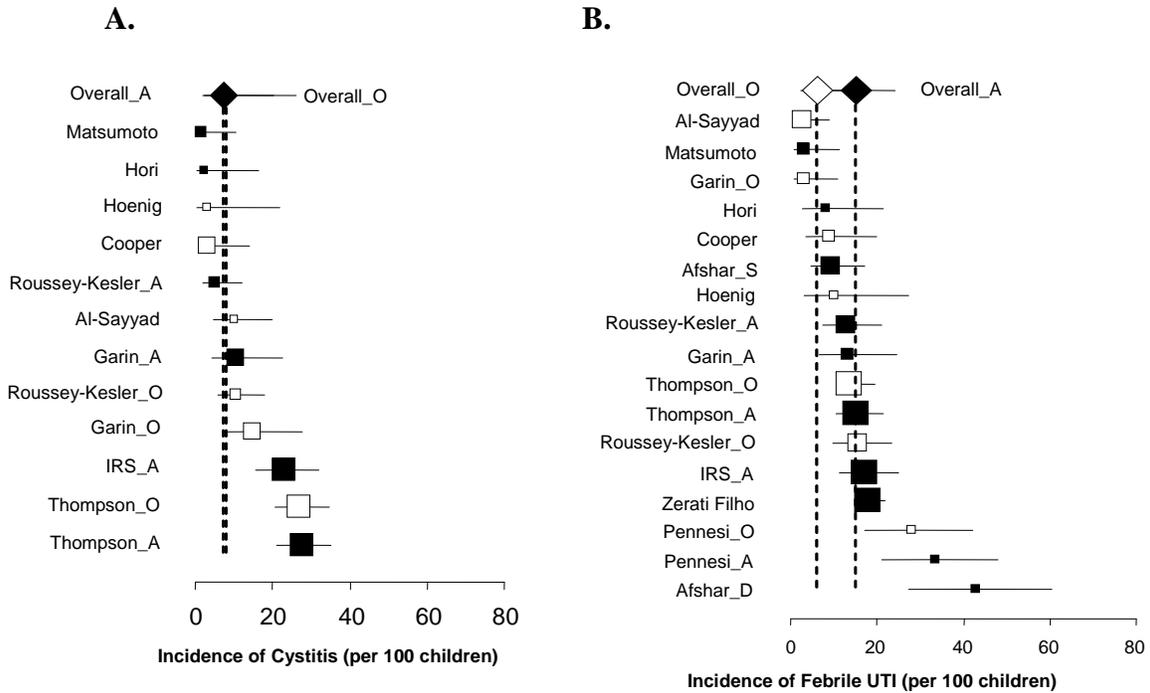
Table 1. UTI incidence in patients with VUR receiving or not receiving CAP.

UTI	N	CAP (95% CI)	N	No CAP (95% CI)
Cystitis	6	7.2 (2.3, 20.3)	6	7.9 (2.1, 26.1)
Febrile UTI	11	15.2 (9.1, 24.2)	8	6.1 (2.3, 15.0)
Not-specified	18	19.0 (13.3, 26.3)	7	17.8 (8.6, 33.3)

Note: N= number of study groups

Although the incidence of cystitis and nonspecified UTIs was similar between those receiving or not receiving CAP, the incidence of febrile UTIs in children receiving CAP was greater than those not receiving CAP. The overall incidence of cystitis and febrile UTI in those receiving or not receiving CAP, as well in the incidences from individual reports, is shown in Figure 5.

Figure 5. Incidence of A) cystitis and B) febrile UTI with CAP (filled) or without CAP (open)

A.

Incidence of Cystitis (per 100 children)

B.

Incidence of Febrile UTI (per 100 children)

Incidence of New Renal Cortical Abnormalities

The incidence of new renal cortical abnormalities identified by scintigraphy after initiation of antibiotic therapy (including those receiving CAP) was 17.1 per 100 children (95% CI: 8.6, 31.1) with VUR (Figure 6). Data regarding new renal scarring in children with VUR treated without CAP were limited.

Figure 6. Incidence of new renal cortical abnormalities during follow-up for VUR

Incidence of Renal Abnormalities (per 100 children)

Resolution of VUR

The overall resolution rate with CAP was 53.2 per 100 children and 67.8 per 100 children (95% CI: 56.8, 77.1) in studies with 25% or fewer males, with the highest rates occurring between 24 and 36 months (range of 12–71 months). At this time, the published resolution curves from the 1997 AUA Guidelines[1] represent the most accurate estimates of resolution; however since few studies have assessed the impact of BBD on resolution, it is not possible to determine whether VUR resolves more slowly in children with BBD.

> **Option: Continuous antibiotic prophylaxis may be considered for the child with a history of urinary tract infection and VUR in the absence of bladder/bowel dysfunction.**
>
> [Based on review of the data and Panel consensus]

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Option: Observational management without continuous antibiotic prophylaxis, with prompt initiation of antibiotic therapy for urinary tract infection, may be considered for the child with VUR in the absence of bladder/bowel dysfunction, recurrent febrile urinary tract infectoins, or renal cortical abnormalities.

[Based on Panel consensus]

Follow-up Management of the Child with VUR

Ongoing monitoring of a child's overall health is necessary. Specific testing related to VUR will depend on the clinical situation and any factors described below that might indicate the potential for ongoing or progressive renal injury.

General

Recommendation: General evaluation, including monitoring of blood pressure, height, and weight is recommended annually.

[Based on Panel consensus]

Recommendation: Urinalysis for proteinuria and bacteriuria is indicated annually, including a urine culture and sensitivity if the urinalysis is suggestive of infection.

[Based on Panel consensus]

Option: The follow-up interval is determined by the likelihood of resolution; for higher grades of VUR, resolution is less likely[1] and therefore a longer interval of follow-up is appropriate.

[Based on Panel consensus]

Imaging

Recommendation: Imaging, including ultrasonography and voiding cystography (radionuclide cystogram or low-dose fluoroscopy, when available) is recommended every 12 to 24 months, with longer intervals between follow-up studies in patients in whom evidence supports lower rates of spontaneous resolution to limit the number of imaging studies (i.e. those with higher grades of VUR (grades III-V; see clinical chapter 2 and 1997 Guidelines), bladder/bowel dysfunction (see clinical chapter 3), and older age). This is to limit the over-all number of imaging studies performed. If an observational approach is being used, follow-up cystography becomes an option.

[Based on review of the data and Panel consensus]

Recommendation: DMSA imaging is recommended when a renal ultrasound is abnormal, when there is a greater concern for scarring (i.e. breakthrough urinary tract infectoin [BT-UTI; see Glossary for description], higher grades III-V of VUR), or if there is an elevated serum creatinine.

[Based on review of the data and Panel consensus]

Option: Follow-up cystography may be done after one year of age in patients with VUR grades I–II; these patients tend to have a high rate of spontaneous resolution and boys have a low risk of recurrent urinary tract infection.

[Based on review of the data and Panel consensus]

Option: A single normal voiding cystogram (i.e. no evidence of VUR) may serve to establish resolution. The clinical significance of grade I VUR, and the need for ongoing evaluation is undefined.

[Based on review of the data and Panel consensus]

Option: Periodic upper tract imaging with renal ultrasound may be done to assess renal growth and the presence of gross renal scarring.

[Based on Panel consensus]

Option: DMSA may be considered for follow-up of children with VUR, to detect new renal scarring, especially after a febrile urinary tract infection.

[Based on review of the data and Panel consensus]

Interventions for the child with a febrile breakthrough UTI

When a febrile breakthrough UTI (BT-UTI) occurs in a child with VUR receiving CAP, consideration of alternative interventions is recommended since there is the potential for renal injury. The clinical manifestations of BT-UTI may not be classic, particularly in the younger child in whom systemic symptoms may predominate.

Recommendation: If symptomatic breakthrough urinary tract infection occurs (manifested by fever, dysuria, frequency, failure to thrive, or poor feeding), a change in therapy is recommended. If symptomatic breakthrough urinary tract infection occurs, the clinical scenario will guide the choice of treatment alternatives; this includes VUR grade, degree of renal scarring, if any, and evidence of abnormal voiding patterns (bladder/bowel dysfunction) that might contribute to urinary tract infection, and parental preferences.

[Based on Panel consensus]

Recommendation: It is recommended that in patients receiving continuous antibiotic prophylaxis with a febrile breakthrough urinary tract infection be considered for open surgical ureteral reimplantation or endoscopic injection of bulking agents for intervention with curative intent.

[Based on Panel consensus]

Recommendation: In patients not receiving continuous antibiotic prophylaxis who develop a febrile urinary tract infection, initiation of continuous antibiotic prophylaxis is recommended.

[Based on Panel consensus]

Option: In patients receiving continuous antibiotic prophylaxis with a single febrile breakthrough urinary tract infection and no evidence of pre-existing or new renal cortical abnormalities, changing to another antibiotic agent is an option prior to intervention with curative intent.

[Based on Panel consensus]

Option: In patients not receiving continuous antibiotic prophylaxis who develop a non-febrile urinary tract infection, initiation of continuous antibiotic prophylaxis is an option in recognition of the fact that not all cases of pyelonephritis are associated with fever.

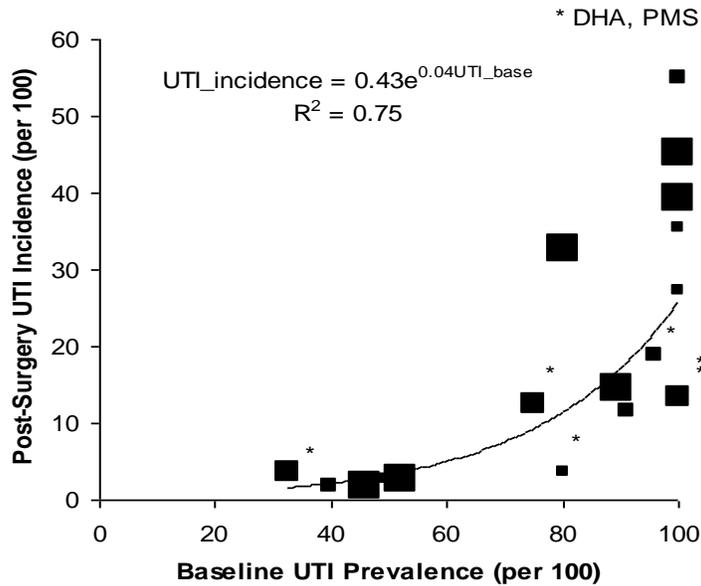[Based on Panel consensus]

Surgical treatment of VUR

Outcomes of open and endoscopic surgical approaches including cure rate, incidence of UTI, renal cortical abnormalities, and adverse events were assessed. Twenty-nine studies evaluated the management of VUR with open surgery, 18 of which reported resolution

rates. The resolution rate per 100 children was 98.1 for open surgery (95% CI: 95.1, 99.1)
and 83.0 for endoscopic therapy (95% CI: 69.1, 91.4) after a single injection of bulking
agent. These studies typically reported reflux status in the first year after intervention.
Data and clinical experience demonstrating the durability of endoscopic therapy for VUR
are limited. The novelty of the treatment has not permitted adequate assessment of its
long-term efficacy in a broad range of patients. While few studies have directly assessed
the long-term durability of open surgery for VUR, clinical experience indicates that
recurrence is rare.[5]

UTI after surgical therapy

Twenty-four studies assessed the incidence of UTI after either endoscopic or open
correction of VUR. The incidence of postoperative febrile UTI was 4.9 cases per 100
children (95% CI: 2.2, 10.4). The rate of postoperative cystitis was higher in the operative
group (15%) versus those receiving CAP (7.2%) and not receiving CAP (7.9%) groups.
Higher preoperative UTI rates were associated with higher postoperative UTI rates. In
studies in which fewer than 60% of children had preoperative UTIs, the postoperative
UTI incidence was 4.6 per 100 children (95% CI: 2.2, 9.6). In studies in which more than
60% of children had preoperative UTIs, the postoperative UTI incidence was 10.2 per
100 children (95% CI: 4.0, 26.2) (Figure 7). It is important to recognize that in the
absence of randomized trials controlled for preoperative UTI incidence comparisons of
outcomes in patients with preoperative and postoperative UTIs may not be reliable.

Figure 7. Incidence of postoperative UTI in relation to the incidence of baseline UTI prevalence in the study population (ecological association)

New renal cortical abnormalities after surgical therapy

The 1997 AUA Guideline[1] found the incidence of new renal cortical abnormalities occurring after surgical versus CAP therapy to be similar; limited useful new data have been reported. In this analysis, the incidence of renal cortical abnormalities after surgery was assessed in 450 patients in four studies with a broad range of 3.0%–38.3%. Due to this extreme variability, which may reflect differences in selection criteria for surgical intervention, it is not possible to determine an overall assessment of the incidence of new renal cortical abnormalities after surgical therapy.

The number of adverse events following endoscopic or open surgery for VUR was low. The overall postoperative obstruction rate calculated from 28 articles was 0.4 (95% CI:

0.2, 1.2) per 100 children. The incidence of postoperative voiding disturbances was 4.2

per 100 children (95% CI: 1.8, 9.2) while the incidence of postoperative contralateral

VUR after unilateral treatment was 9.6 per 100 children (95% CI: 7.5, 12.2).

Option: Surgical intervention for VUR, including both open and endoscopic methods, may be used. Prospective randomized controlled trials (RCTs) have shown a reduction in the occurrence of febrile urinary tract infections in patients who have undergone open surgical correction of VUR as compared to those receiving continuous antibiotic prophylaxis.[5, 6]

[Based on review of the data and Panel consensus]

Management following resolution of VUR

Although there are no data with which to assess a specific follow-up program, it is

recognized that the presence renal injury is associated with a higher risk of later health

effects. While these risks may be low, they are known to increase with the duration of

follow-up.

Option: Following the resolution of VUR, either spontaneously or by surgical intervention and if both kidneys are normal by ultrasound or DMSA scanning, general evaluation, including monitoring of blood pressure, height, and weight, and urinalysis for protein and urinary tract infection, annually through adolescence is an option.

[Based on Panel consensus]

Recommendation: Following the resolution of VUR, either spontaneously or by surgical intervention, general evaluation, including monitoring of blood pressure, height, and weight, and urinalysis for protein and urinary tract infection, is recommended annually through adolescence if either kidney is abnormal by ultrasound or DMSA scanning.

[Based on Panel consensus]

Recommendation: With the occurrence of a febrile urinary tract infection following resolution or surgical treatment of VUR, evaluation for bladder/bowel dysfunction or recurrent VUR is recommended.

[Based on Panel consensus]

Recommendation: It is recommended that the long-term concerns of hypertension (particularly during pregnancy), renal functional loss, recurrent urinary tract infection, and familial VUR in the child's siblings and offspring be discussed with the family and communicated to the child at an appropriate age.

[Based on Panel consensus]

Summary

An association between VUR and renal injury was demonstrated in this meta-analysis after reviewing studies evaluating renal cortical abnormalities on DMSA scanning at diagnosis and examination of specific endpoints secondarily related to renal damage such as hypertension, renal insufficiency, and somatic growth impairment. These observations support therapeutic management of VUR in children in order to reduce the risk of pyelonephritis and potential permanent renal injury.

Spontaneous resolution of VUR does occur and remains the basis for expectant management where CAP is used to prevent potentially injurious UTI. The efficacy of CAP in preventing febrile UTI or renal injury remains uncertain. There have been few studies comparing the outcomes of CAP in children with VUR until recently and the generalizability of these studies to the broader patient population has not been established. One retrospective study showed no difference in the occurrence of UTI or scarring after discontinuing CAP.[7] Three recently published studies have addressed the question of the clinical benefit of CAP in children with VUR.[8-10] All were prospective, multicenter, randomized studies in children with their first UTI. In the study by Garin et al.,[8] the wide range of ages (from 1 month to 18 years) and the inability to define specific outcomes for the subgroups with the criteria used to assess other reports limited its utility; it was therefore not included in this meta-analysis. For studies included in this meta-analysis, Roussey-Kessler et al.[10] showed a benefit for CAP in boys with grade III VUR but did not address higher grades while Pennesi et al.[9] included children with grade IV VUR, but in limited numbers. In these studies there was no assessment of voiding patterns and medication compliance, there was significant heterogeneity in the patient

population raising questions about the variation in selection criteria, and in one study UTIs were documented by bag urines. At this point, it is uncertain whether there is a benefit to the use of CAP in children diagnosed with VUR following a first febrile UTI or for patients with VUR grades III, IV and V.

The Cochrane analyses of the use of CAP in treatment of VUR have also been cited as demonstrating the lack of benefit with the use of CAP.[11, 12] These systematic reviews have served as the basis for the recent publication of the National Institute for Health and Clinical Excellence Guidelines related to evaluation and management of UTI in children for the National Health Service in Great Britain.[13] However, the Cochrane systematic reviews include only RCTs, which is a major limitation since very few studies are included.

From a practical standpoint, a cautious approach should be taken in the management of children with low-grade VUR pending the availability of data from recently reported RCTs[14] and including the Swedish Reflux Study (to be published in the Journal of Urology in 2010; reported at the International Conference on Vesicoureteral Reflux in Children, Goteborg, 2009), and the Randomized Intervention for Children with Vesicoureteral Reflux [RIVUR] study (www.rivur.net)). Thus our Guideline includes the option of managing children without the use of CAP while maintaining careful observation. Continuing the use of CAP in children with grades II-V VUR seems prudent until more data are available.

If there is indeed a lack of preventative benefit with CAP for acute pyelonephritis and renal injury in children with VUR, one may question the value of treating, or even diagnosing, VUR. Alternately, the implication may be that every child with VUR should undergo surgical intervention using open or endoscopic methods. Neither can be justified as yet in routine clinical practice for all patients. Selection criteria have not been defined nor validated for those patients in

whom a non-interventional approach is appropriate. It would seem imprudent to discard an approach that evolved from careful clinical observation and shows no evidence of harm, until more robust data are available in terms of the certainty of the safety of non-interventional management of VUR, and in whom this approach is appropriate.

Observational management without the administration of CAP (with prompt initiation of antibiotic therapy for acute UTI), is currently under investigation, so no recommendations regarding this form of therapy can be made at this time. Decisions regarding choice of treatment depend on a number of factors such as patient age, VUR grade, the presence of scarring at diagnosis, and parental preferences. The likelihood of resolution of VUR by observational, endoscopic, and open surgical therapy should be factored into the decision-making process. Higher VUR grades and the presence of scarring would more strongly favor a curative intervention to limit risk of further damage in a child with reduced renal reserve.

There are no data assessing the value of any particular follow-up regimen in children with ongoing or resolved VUR. Any Guideline must be based on a clinical judgment as to the potential for late effects of renal injury and UTI, and the ability to intervene if these effects occur. The principal concerns include the development of hypertension and renal insufficiency, as well as acute pyelonephritis from cystitis or bacteriuria. The few long-term studies on the impact of scarring, albeit in a selected population, include that of Smellie et al.,[4] in which the incidence of late hypertension, renal insufficiency and complications of pregnancy were associated with the severity of scarring and the duration of follow-up, and of Martinell et al.,[15] in which pyelonephritis during pregnancy was related to renal scarring and the prior incidence of UTI. It should be noted that the National Heart, Lung and Blood Institute and the American Academy of Pediatrics recommend that a blood pressure determination should be made in all children over the

age of 3 years.[16] This recommendation is for all children, not just those with demonstrable renal injury related to VUR, and is applicable to any child with major illness, including pyelonephritis.

References

1.   Elder, J. S., Peters, C. A., Arant, B. S., Jr. et al.: Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. J Urol 1997; **157:** 1846.

2.   Polito, C., La Manna, A., Mansi, L. et al.: Body growth in early diagnosed vesicoureteric reflux. Pediatr Nephrol 1999; **13:** 876.

3.   Polito, C., Marte, A., Zamparelli, M. et al.: Catch-up growth in children with vesico-ureteric reflux. Pediatr Nephrol 1997; **11:** 164.

4.   Smellie, J. M., Prescod, N. P., Shaw, P. J. et al.: Childhood reflux and urinary infection: a follow-up of 10-41 years in 226 adults. Pediatr Nephrol 1998; **12:** 727.

5.   Jodal, U., Smellie, J. M., Lax, H. et al.: Ten-year results of randomized treatment of children with severe vesicoureteral reflux. Final report of the International Reflux Study in Children. Pediatr Nephrol 2006, **21:** 785.

6.   Jodal, U., Koskimies, O., Hanson, E. et al.: Infection pattern in children with vesicoureteral reflux randomly allocated to operation or long-term antibacterial prophylaxis. The International Reflux Study in Children. J Urol 1992, **148:** 1650.

7.   Thompson, R. H., Chen, J. J., Pugach, J. et al.: Cessation of prophylactic antibiotics for managing persistent vesicoureteral reflux. J Urol 2001, **166:** 1465.

8.   Garin, E. H., Olavarria, F., Garcia Nieto, V. et al.: Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics 2006, **117:** 626.

9.   Pennesi, M., Travan, L., Peratoner, L. et al.: Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. Pediatrics 2008, **121:** e1489.

10.   Roussey-Kesler, G., Gadjos, V., Idres, N. et al.: Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. J Urol 2008, **179:** 674.

11.   Hodson, E. M., Wheeler, D. M., Vimalchandra, D. et al.: Interventions for primary vesicoureteric reflux. Cochrane Database Syst Rev 2007**:** CD001532.

12.   Wheeler, D. M., Vimalachandra, D., Hodson, E. M. et al.: Interventions for primary vesicoureteric reflux. Cochrane Database Syst Rev 2004**:** CD001532.

13.   NCCWCH: Urinary Tract Infection in Children - diagnosis, treatment and long-term management. London: RCOG Press, p. 148, 2007

14.   Craig, J. C., Simpson, J. M., Williams, G. J. et al.: Antibiotic prophylaxis and recurrent urinary tract infection in children. N Engl J Med 2009, **361:** 1748.

15.   Martinell, J., Claesson, I., Lidin-Janson, G. et al.: Urinary infection, reflux and renal scarring in females continuously followed for 13-38 years. Pediatr Nephrol 1995, **9:** 131.

16.   National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and, A.: The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004, **114:** 555.