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Review article

Summary of recent AUA guidelines for the management of vesicoureteral reflux in children

M. Moradi , D.A. Diamond *

Boston Children Hospital, Harvard Medical School, 300 longwood ave., Boston, MA, United States

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Abstract
VUR is a common condition and it is a predisposing factor for pyelonephritis, and reflux nephropathy, which can cause end stage renal disease in children. Given the consequences and sequelae of UTI and VUR, and due to lack of consensus regarding management of this common condition, the American Urological Association (AUA) developed treatment guidelines for children with VUR in 1997 and 2012 to help physicians better manage children with VUR. In this review, the summary of the 1997 and 2012 AUA guidelines are discussed with a focus on the 2012 report. Recommendations about evaluation and management of children under and above one year with VUR, with and without bladder/bowel dysfunction, screening of siblings of patients with VUR, screening of the neonate/infant with prenatal hydronephrosis, and follow up of the children with VUR are discussed in this review. The identification and management of VUR in these groups, provide the potential opportunity to prevent renal damage and decrease the risk of UTI and pyelonephritis. According to these guidelines, risk assessment of renal injury/scarring in the individual patient based upon clinical factors is critical, and interventions should be appropriate to the risk profile. Informing families and healthcare providers of the potential risk of pyelonephritis and renal scarring and allowing them to participate in decision making is considered important.

Introduction

Vesicoureteral reflux (VUR) refers to retrograde flow of urine from the bladder into the ureter and collecting system of the kidney [1]. VUR is a common condition: between 3 and 5% of girls and 1–2% of boys, experience urinary tract infection (UTI) before puberty [2]. VUR is associated with higher rates (57%) of febrile UTI [1] and approximately 30–40% of children with UTI have reflux [3]. Reflux is a predisposing factor for pyelonephritis, and reflux nephropathy. The two important late complications of reflux nephropathy are end stage renal disease and renin-mediated hypertension [4]. So identification and management of VUR provide the potential

* Corresponding author. Tel.: +1 6173557796.
E-mail address: David.Diamond@childrens.harvard.edu (D.A. Diamond).
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opportunity to prevent renal damage and decrease the risk of UTI and pyelonephritis. Currently, there are several treatment options including, observation, continuous antibiotic prophylaxis, and open, endoscopic or laparoscopic surgery.

Because of the lack of consensus regarding management of this common condition, the American Urological Association (AUA) developed treatment guidelines for children with VUR in 1997 and 2012 to help physicians better manage children with VUR.

In this review, the 1997 and 2012 AUA guidelines are discussed with a focus on the 2012 report.

Initial evaluation of VUR

General evaluations

The somatic growth curve is one of the best global parameters of renal health in children [1]. Many children with VUR and UTI who fall below the normal growth curve, have normalized with successful suppression of pyelonephritis with continuous antibiotic prevention or surgical correction of reflux. So height and weight evaluation of these patients is necessary [5,6]. Furthermore, VUR is a primary cause of significant hypertension in children so measurement of BP should be part of the primary evaluation of these patients [1].

Laboratory tests

Urinalysis and urine culture, are important for confirmation of bacteriuria and UTI, and also allow the diagnosis of hematuria and proteinuria. Serum creatinine measurement is important in evaluation of renal function and GFR estimation [1].

Assessment of upper urinary tract

The goal of upper tract imaging is the assessment of renal scarring and diagnosis of associated urinary tract anomalies. Most commonly achieved with ultrasonography and DMSA renal scan. Renal sonography is useful for evaluation of hydronephrosis, renal duplication, and gross renal parenchymal abnormalities. The surface areas of the kidney on renal sonography correlate with differential renal function [7]. There is good correlation between sonographic renal length and scintigraphic renal size [8]. However, following an episode of pyelonephritis, renal scarring usually is apparent on DMSA, within 3 months, but may not be apparent on sonography until 1–2 years later. So, the gold standard for assessing renal parenchymal function is DMSA [1]. If the initial DMSA demonstrated pyelonephritis, the follow-up scan at 6 month may show a scar [9]. The presence of reflux increases risk of permanent scarring after pyelonephritis. In addition greater number of UTIs, correlate with more scarring.

Assessment of lower urinary tract

The goal of lower urinary tract assessment is to assess bladder emptying, anatomic abnormalities of bladder and urethra, and evaluation of VUR. This information may be obtained with Voiding Cysto-Urethrography (VCUG) [1]. The RNC (radionuclide cystography) is an alternative, low dose test that allows VUR diagnosis but with limited anatomic detail. Cystoscopy and Urodynamic study may be beneficial in children with voiding dysfunction [1].

Management of the infants under 1 year with VUR

Without renal scarring at diagnosis. Infants with grades I–V reflux should be treated initially with continuous antibiotic prophylaxis. If uncomplicated reflux continues, antibiotic prophylaxis should be continued. For patients with persistent Grades I–II reflux, there is no consensus regarding the role of continued antibiotic therapy, periodic cystography, or surgery. For patients with persistent unilateral Grades III–IV reflux, surgical repair is the preferred option. Patients with persistent bilateral Grades III–IV reflux or Grade V reflux should undergo surgical repair [10].

With renal scarring at diagnosis. Infants with Grades I–IV reflux and renal scarring should be treated initially with continuous antibiotic prophylaxis. In infants with Grade V reflux and scarring, continuous antibiotic prophylaxis is the preferred option for initial treatment, and surgical repair is a reasonable alternative. In patients with persistent Grades I–II reflux, there is no consensus regarding the role of continued antibiotic prophylaxis, periodic cystography, or surgery. In boys with persistent unilateral Grades III–IV reflux, surgical repair is the preferred option. Boys with persistent bilateral Grades III–IV reflux, girls with persistent Grades III–IV reflux, and boys and girls with persistent Grade V reflux should undergo surgical repair [10].

The management of infants with VUR has become increasingly controversial due to many systematic reviews, which support the protective role of circumcision and studies that question the time-honored value of prescribing continuous antibiotic prophylaxis (CAP) and a shift to early treatment by endoscopic injection therapy [11]. In order to decrease the morbidity of UTI and the risk of renal injury, treatment of VUR includes the options of observation, continues antibiotic prophylaxis and curative interventions as recommended.

Due to the greater morbidity from recurrent urinary tract infection, continuous antibiotic prophylaxis is recommended for the child less than one year of age with VUR with a history of a febrile urinary tract infection. If there was no history of febrile urinary tract infection, continuous antibiotic prophylaxis is recommended for the child less than one year of age with VUR grades III–V who is identified through screening. This approach is optional for children with grades I–II who are diagnosed through screening. Because of the increased risk of urinary tract infection in boys who are not circumcised, circumcision of the male child with VUR may be considered. There is not sufficient data to support this recommendation definitely, but it is better to make parents aware of the potential benefit [11].

Management of the infants over 1 year with VUR

Without renal scarring at diagnosis. Continuous antibiotic prophylaxis is the best initial option for preschool children with Grades I–II reflux or unilateral Grades III–IV reflux and the preferred option in children with bilateral Grades III–IV reflux. In patients with unilateral Grade V reflux, continuous antibiotic prophylaxis is the preferred option for initial treatment, although surgical repair is a reasonable alternative. In patients with bilateral Grade V reflux, surgical repair is the preferred option and continuous antibiotic prophylaxis is a reasonable alternative [10].

If uncomplicated reflux continues, antibiotic prophylaxis should be continued. In children with persistent Grades I–II reflux, there

is no consensus regarding the role of continued antibiotic therapy, periodic cystography or surgery. Surgery is the preferred option for children with persistent Grades III–IV reflux. Patients with persistent Grade V reflux should undergo surgical repair [10].

With renal scarring at diagnosis. Preschool children with scarring at diagnosis and either Grades I–II reflux or unilateral Grades III–IV reflux should be treated initially with continuous antibiotic prophylaxis. Antibiotic therapy is the preferred option in children with bilateral Grades III–IV reflux and scarring, and surgical repair is a reasonable alternative. Surgery is the preferred option for patients with unilateral Grade V reflux. Patients with bilateral Grade V disease and scarring should undergo surgical repair as initial treatment [10].

In children with uncomplicated reflux, antibiotic prophylaxis should be continued. In patients with persistent Grades I–II reflux after this period of prophylaxis, there is no consensus regarding the role of continued antibiotic prophylaxis, periodic cystography, or surgery. Girls with persistent Grades III–IV reflux and boys with persistent bilateral Grades III–IV reflux should undergo surgical repair. Surgery is the preferred option for boys with persistent unilateral Grades III–IV reflux and girls with bilateral Grades III–IV reflux. For patients with persistent Grade V reflux, surgical repair is the preferred option [10].

If symptoms of breakthrough urinary tract infection, such as fever, dysuria, frequency, failure to thrive, or poor feeding develop, therapy should be changed. Age, VUR grade, degree of renal scarring, and evidence of abnormal voiding patterns, and parental preferences can guide the physician to choose the best treatment [11].

For patients on continuous antibiotic prophylaxis with a febrile breakthrough urinary tract infection open surgical ureteral reimplantation or endoscopic injection of bulking agents is recommended. For patients not receiving continuous antibiotic prophylaxis who develop a febrile urinary tract infection, continuous antibiotic prophylaxis should be initiated. In recent patients who develop a non-febrile urinary tract infection, initiation of continuous antibiotic prophylaxis is optional. For patients receiving continuous antibiotic prophylaxis, who develop a single febrile breakthrough urinary tract infection and no pre-existing or new renal cortical abnormalities, the antibiotic agent, should be changed prior to definitive intervention [11].

In summary, for children over one year with a history of UTI and VUR, in the absence of dysfunctional elimination syndrome, continuous antibiotic prophylaxis is a viable option. Observational management without continuous antibiotic prophylaxis, with prompt antibiotic therapy for UTI may be considered [11].

Management of children with VUR and bladder/bowel dysfunction

BBD (bladder/bowel dysfunction) refers to children with abnormal storage and/or emptying. It includes lower urinary tract symptoms such as urge incontinence, voiding postponement, and voiding dysfunction, and may also include abnormal bowel patterns, such as constipation and encopresis. The most common cause is failure of relaxation of the external sphincter and/or pelvic floor muscles which lead to high voiding pressures and incomplete evacuation. The result of incomplete emptying of the bladder may predispose the child to UTI [11].

Symptoms indicative of bladder/bowel dysfunction should be explored in the initial evaluation. In this situation, treatment of bladder/bowel dysfunction is indicated, preferably before any surgical intervention for VUR. There are insufficient data to recommend a specific treatment regimen for bladder/bowel dysfunction, but possible treatment options include: behavioral therapy, biofeedback, anticholinergic medications, alpha blockers, and treatment of constipation. Response of bladder/bowel dysfunction to treatment should be monitored to determine whether treatment should be maintained or modified. Based on the results of a meta-analysis, children with BBD are associated with decreased reflux resolution at 24 months, and a lower rate of correction after endoscopic surgery but not open surgery. The incidence of baseline renal cortical abnormalities in children with BBD was higher than in infants without BBD [11].

In summary, due to the increased risk of urinary tract infection, continuous antibiotic prophylaxis is recommended for these children. However, they are associated with more UTIs on CAP both before and after surgical correction, so these children should undergo an assessment and appropriate treatment of voiding and bowel habits. Correction of BBD should also be undertaken prior to surgical therapy, but there are some clinical conditions for which intervention is considered imperative as an initial step including: uncontrolled breakthrough UTIs or progressive renal damage. In that setting, open surgical correction appears to have the greatest likelihood of cure [11].

Screening of siblings and of patients with VUR

The incidence of VUR in the general population is about 1% because it is a polygenic genetic disorder [4]. 100% concordance in identical twins and 35–50% prevalence in fraternal twins is reported [12]. Cystography of siblings and offspring of patients with VUR has shown a high prevalence of VUR [13]. The goal of screening of these groups is detection of a population at risk and early treatment in order to reduce the risk of adverse outcomes associated with VUR.

In the 1997 VUR guideline, a proposed future research goal was to determine the impact of sibling and offspring screening with early medical or surgical treatment on the risk of these outcomes. There were some questions to answer: Does screening and treatment prevent UTI? Does screening and treatment prevent renal damage? Is medical therapy effective in screened populations? In order to answer these questions, Skoog et al. performed a meta-analysis of 3040 children screened with a cystogram (2796 siblings, and 244 offspring) and the effects of treatment were assessed in regards to resolution, urinary infections, and renal scarring [14]. The prevalence of VUR was 27.4% in siblings. The rate of renal damage in asymptomatic sibling (without UTI) was 14.4% and for screened siblings, some of whom were symptomatic was 22.8%, suggesting that renal damage may be preventable in some cases. In addition, there is no RCT nor prospective cohort studies that compare outcome in screened and non-screened siblings. So, the 2012 AUA guideline, recommended screening in at risk cases. Any evidence of renal scarring or renal size asymmetry on ultrasound or a history of urinary tract infection in the sibling who has not been tested, are indications for evaluation, so that a voiding cystourethrogram or radionuclide cystography is recommended for these

groups of patients. For other asymptomatic siblings, an observational approach without screening and prompt treatment of any acute urinary tract infection and subsequent evaluation for VUR has been recommended AUA Guideline [11].

Renal ultrasonography screening is helpful for the detection of significant renal scarring, and the potential further risk of VUR [11].

Screening the offspring of patients with VUR can be regarded similarly to the screening of siblings [11].

Screening of the neonate/infant with prenatal hydronephrosis

Prenatal hydronephrosis (PNH) is defined as renal pelvic diameter $\geq$5 mm during the second trimester and $\geq$8 mm during the third trimester of pregnancy [15]. The goal of postnatal evaluation is to diagnose and manage vesicoureteral reflux before secondary damage may occur from urinary tract infection.

In Skoog et al's meta-analysis study involving 6579 infants with PNH; ultrasonography and VCUG were performed during the neonatal period and first 3 months of life, respectively [14]. This study demonstrated, VUR detected in an average of 16.2% of patients, occurring more frequently in female than male ($p = 0.022$). The incidence of VUR grade was the same (33%) between SFU (Society of Fetal Urology) hydronephrosis Grade 1–2, Grade 3, and Grade 4–5. The incidence of reflux in the contralateral nondilated kidney was 4.1%. The VUR prevalence was independent of renal pelvic diameter (RPD) [11].

Skoog et al. noted that the incidence of renal cortical abnormality before UTI was 21.8% per patient and 32.3% per renal unit. Only 8 studies reported on UTI during the post screening period. The incidence of UTI averaged 4.2% in cases with reflux [14]. In summary, the rate of reflux is approximately 16% (in compare to 1% of the general population) and the incidence is independent of prenatal RPD, and may be detected in non-dilated renal units. Reflux is high grade in two-thirds of patients. Renal cortical abnormalities occurred in nearly 50% of those with grades IV–V. So, these considerations potentially support postnatal cystography in all neonates with PNH. However, the lack of prospective studies demonstrating the benefit of reflux detection in asymptomatic neonates and recent data from prospective studies that question efficacy of antibiotic prophylaxis to prevent UTI make screening cystography an option, rather than a recommendation [11]. Therefore, voiding cysto-urethrogram is recommended for children with high-grade (Society of Fetal Urology grade 3 and 4) hydronephrosis, hydroureter or an abnormal bladder on ultrasound (late term prenatal or postnatal), or those who develop a urinary tract infection on observation [11].

For children with prenatally detected hydronephrosis (SFU grade 1 or 2) an observational approach without screening for VUR may be indicated. In this situation, a UTI mandates treatment followed by VCUG to screen for VUR [11].

Follow up of the children with VUR

Recommendation

The follow up interval is dependant upon likelihood of resolution, as higher grades of reflux have lower resolution rates than lower grades, justifying a longer interval of follow up for these patients as well as those in whom evidence supports lower rates of spontaneous resolution such as older patients and those with bladder/bowel dysfunction [11].

In children with VUR yearly measurement of blood pressure, height and weight is recommended. Also, a yearly urinalysis and urine culture for evaluation of proteinuria and infection and ultrasonography for evaluation of renal growth and scarring is recommended. Depending upon the prior reflux grade, a 12–24 month periodic radionuclide cystography (RNC) is indicated, but this is optional for grade 1 reflux. A single normal voiding cystogram is acceptable to demonstrate resolution [11].

There are some indications for follow up with DMSA imaging for these patients including: abnormality in renal ultrasonography, concern for renal scarring such as breakthrough pyelonephritis, elevated serum creatinine and high grade reflux (grade III–V) [11].

Conclusions

VUR remains a clinical challenge and there is no definitive algorithm to manage reflux. It is necessary to look at the total patient with special attention on voiding function, age, grade of reflux, history of UTI, presence of renal abnormalities and scarring, and parental preferences. Hence, risk assessment of renal injury/scarring in the individual patient based upon clinical factors is critical, and interventions should be appropriate to the risk profile. Informing families and healthcare providers of the potential risk of pyelonephritis and renal scarring and allowing them to participate in decision making is considered important.

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