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EDUCATIONAL REVIEW

Primary vesicoureteral reflux; what have we learnt from the recently published randomized, controlled trials?

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Abstract

In recent years, progress has been made on understanding the relationship between vesicoureteral reflux (VUR) and urinary tract infection (UTI). The findings on recent prospective, randomized, controlled studies have questioned the conventional VUR clinical significance and, therefore, have challenged the traditional diagnostic and therapeutic recommendations. These new studies have redefined the pathogenic role of vesicoureteral reflux in UTI as well as have disputed the routine use of urinary antibiotic prophylaxis to prevent UTI and renal damage in VUR patients. The time to overinvestigate and treat the vast majority of otherwise healthy children who have an uncomplicated UTI with long-term antibiotic prophylaxis seems to be over. Is there a role of severe VUR in the development of chronic renal disease and renal failure? New ideas are needed to answer these questions with the goal to avoid repeating past mistakes when therapeutic choices were based on expert opinions rather than facts.

Keywords Vesicoureteral reflux · Urinary tract infection · Urinary antibiotic prophylaxis

Definition

Vesicoureteral reflux (VUR) is defined as the retrograde movement of urine from the bladder into the ureter(s). This retrograde flow of urine can distend (dilating VUR) or not (non-dilating VUR) the pyelocaliceal system. This review will only address the clinical significance and medical therapy of primary VUR in children.

The diagnosis and clinical significance of VUR in children were defined in the 1960. Since then, VUR in children has been the subject of numerous publications, but the past 12 years has seen randomized controlled trials (RCTs) on VUR that have questioned its conventional clinical significance and have disputed the traditional diagnostic and therapeutic recommendations.

Key summary facts
1. Non-dilating VUR does not predispose to UTI, acute pyelonephritis (APN), and renal parenchymal damage.
2. Urinary antibiotic prophylaxis is not routinely indicated in healthy children with non-dilating VUR.
3. The role of severe VUR in the pathogenesis of UTI, APN, and the use of urinary antibiotic prophylaxis needs to be defined.

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Diagnosis

Voiding cystourethrogram (VCUG) is the gold standard for the diagnosis and grading of VUR. Up to a few years ago, VCUG was indicated after first febrile urinary tract infection (UTI) regardless of the severity of the involvement. Based on "new evidence demonstrating antimicrobial prophylaxis not to be effective as presumed previously for VUR," the National Institute for Health and Care Excellence in the United Kingdom (NICE) (2007) [1] and the American Academy of Pediatrics(AAP) (2011) [2] have recommended that VCUG should not be performed routinely after first, febrile, UTI in patients less than 24 months old unless renal ultrasound (RUS) reveals abnormalities ("hydronephrosis, scarring, or other findings that would suggest either high-grade VUR or obstructive uropathy"), or other atypical or complex clinical circumstances such as atypical/recurrent febrile UTI. The AAP has reaffirmed the same guidelines in 2015. In contrast, the American (2012) and European (2015) Urological Associations have continued to recommend performing a VCUG after first febrile UTI in children less than 2 years of age [3, 4].

Lee et al. presented the American experience on requesting VCUG after the NICE and AAP guidelines were published. These authors showed that in children 0–2 years old, VCUG utilization did not decrease after the 2007 NICE guidelines were announced but did significantly decrease after the 2011

AAP guidelines were published. In children 3–10 years old, VCUG utilization decreased during the entire study period [5].

On VCUG, following a UTI, 80% of patients present grades II and III VUR. Type IV or V and grade I each represent roughly 10% of the population of patients with VUR. The distribution varies with age likely reflecting the natural course of the condition, sex, and the reason to request VCUG (UTI, congenital hydronephrosis).

Prevalence

The prevalence of VUR in a population without a history of UTI is rather low. When data from different studies were combined, VUR was present in only 4 of 1095 healthy neonates and children [6]. Bailey reported a prevalence of 0.4 to 1.8% in children without a history of UTI [7].

Depending of age and method of study, 34 to 45% of siblings and first-order relatives of VUR patients do present VUR. A history of UTI is usually absent in 75% of the siblings [8]. A single dominant gene best explains the transmission of the trait. This gene in cases of primary VUR has not been identified though it is different than the one observed when VUR is a component of a syndrome [9]. The AAP, in contrast to the American Urological Association (AUA), does not recommend VCUG to routinely screen VUR patients' siblings [2].

Vesicoureteral reflux in patients with UTI is more prevalent in younger ages. In neonates, the prevalence has been found to range from about 50 to 70%, but VCUG was requested in some of these neonates because of congenital hydronephrosis rather than UTI. The prevalence declines with age. In one study, it was 10% by age 12 years [10]. Vesicoureteral reflux undergoes spontaneous improvement and resolution with time (see below). This explains the decrease prevalence with age. VUR prevalence was found 10 times higher in white than Afro-American girls evaluated for symptomatic UTI [11].

Natural course

Vesicoureteral reflux improves and resolves with time. The spontaneous resolution is higher in grades I and II and less in those patients with dilated VUR (grades III to V). According to the South West Pediatric Nephrology Study Group, the resolution rate was 80% of grade II ureters after 5 years of follow-up. During the same period of observation, only 46% of ureters with grade III had resolved [12]. In the report of the International Reflux Study that appeared about the same time [13], unilateral reflux was shown to cease in 38% of patients with grade IV reflux and in 46% of those with grade III in patients randomly allocated to the medical arm of the study after 5 years of follow-up. In the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) study, VUR had resolved in 50% of children (no VUR grading given) at the end of the 2 years follow-up [14]. Pennisi, saw persistence of grade IV VUR in 52% of patients on prophylaxis at the end of 4 years of follow-up [15].

Time to resolution varies according to the degree of VUR. Schwab estimated that median years to resolution was 2.7 years for grade I, 3.1 years for grade II, 4.5 years for grade III, and 9.5 years for grade IV [16].

How often does VCUG need to be repeated in a patient known to have VUR? VCUG is an uncomfortable and sometimes traumatic procedure. Thus, a review of recent studies suggests that for VUR grade I and II, since VUR does not get worse with time, there is no need to repeat the VCUG but to continue aggressively treating episode(s) of recurrent UTI. In the case of grade III to V, especially grade IV and V, and knowing that sterile reflux does not cause renal damage, VCUG may be repeated every 2 to 3 years to look for spontaneous resolution while continuing observing the upper tract if recurrent acute pyelonephritis (APN) is documented.

Clinical significance

For many years, VUR has been considered a risk factor for UTI, APN, and renal parenchymal damage. Bacteria reaching the bladder from the urethra are not completely evacuated after each voiding because of urine returning from the ureter(s) in the presence of VUR. Urine, which is considered an excellent culture medium, is present at all times in the bladder, allowing bacterial multiplication. During voiding, VUR transports infected urine to the renal parenchyma, especially in patients with intrarenal reflux. The concept of VUR as a risk factor, developed in the 1960th, is rather entrenched in the medical community and has led to the clinical practice of obtaining a VCUG to evaluate for the presence of VUR in children who have had a UTI and to prevent further UTI and, therefore, renal damage with the long-term administration of daily low-dose antibiotics or the surgical correction of VUR.

The concept of VUR as a risk factor for UTI, APN, and renal scars is reviewed.

1. Does VUR predispose to UTI? Until recently, this assumption was accepted based on expert opinions and never validated. Works by Kunin [17] and Elo [18] demonstrating that the rate of recurrent UTI in VUR patients was no higher than the one observed in patients without VUR were overlooked. Even now, no study has specifically addressed this question, but some answers can be obtained analyzing data available in the randomized controlled trials (RCTs) on VUR and the use of urinary antibiotic prophylaxis published since 2006 [14, 15, 19–24].

Urinary tract infection recurrent rate in VUR patients compared to patients without VUR with both groups not receiving urinary antibiotic prophylaxis has been gathered from two RCTs [19, 20]. The group with VUR consisted of 179 patients and 27 of them had recurrence of febrile UTI (15.08%), while patients without VUR were 175 and 24 of them had a UTI recurrence (13.7%). The difference was not statistically significant (p = 0.39). In 2015, the members of the RIVUR study called our attention to an ongoing study (Careful Urinary Tract Infection Evaluation [CUTIE]) that would evaluate the same issue, but no data have been published yet. The available data, therefore, do not support the concept that VUR predisposes to UTI.

2. Does VUR increase the risk of APN and renal scar? During voiding, infected urine may reach the renal parenchyma. Patient may develop APN that poorly or delayed treated can result in renal scars. Supporting this chain of events, there is a greater number of abnormal technetium-99 m–labeled dimercaptosuccinic acid (DMSA) renal scans in patients with higher VUR grades. Snodgrass have reported that focal defects were present in 50% of patients with grades IV but none with grade II [25]. However, without DMSA scintigraphy data obtained before UTI, the distinction between congenital and acquired damage is impossible to make with absolute certainty, and, therefore, Snodgrass finding of focal defects in grades IV and V may overstate acquired renal damage [25].

Febrile UTI episodes have been attributed to APN. However, febrile UTI does not necessarily mean the presence of APN. Only 60% of the children with febrile UTI in Hoberman study presented focal defects on DMSA scan obtained at the time of infection compatible with APN [26]. In the RCT studies, DMSA renal scan was obtained at baseline and repeated at the end of the trial. During the follow-up, if there was a febrile UTI recurrence, no DMSA scintigraphy that could confirm the presence of APN was requested in all except one of the published RCTs [19]. In this study, DMSA renal scan was performed at each episode of febrile recurrent UTI during the year of follow-up. In the non-prophylaxis VUR group of 58 patients, 1 episode of APN was reported. In the non-prophylaxis, no VUR group of 60 patients, only 2 episodes of APN were recorded. The numbers are small, but they suggest no difference in the recurrence of APN between VUR and no VUR groups. The same study shows that two patients in the non-prophylaxis VUR group developed renal scar, while four in the non-prophylaxis no VUR group did so.

Finally, the presence of bacteria in the upper urinary tract during voiding in VUR patients does not always imply renal parenchyma involvement as it was documented in the study by Hansson et al. on VUR and asymptomatic bacteriuria [27].

We conclude that there is no convincing evidence that VUR predispose to APN or renal scars in patients with no dilating VUR. There is the need for better studies documenting APN in patients with grades IV and V VUR to support the assumption that these VUR grades are risk factors for APN.

Long-term antibiotic prophylaxis for VUR

Management of children with VUR has been directed at preventing UTI recommending either antibiotic prophylaxis or surgical correction of VUR. Only data about the use of antibiotic prophylaxis in VUR patients are reviewed.

1. Does antibiotic prophylaxis decrease UTI recurrence rate? The effect of urinary prophylaxis in patients without VUR is available from data gathered from three recent RTCs [19–21]. Two hundred ninety-three patients received prophylaxis and 256 placebo or no antibiotic and were followed for a year. In the prophylaxis group, 23 children (7.8%) and 30 in the no treatment group (11.7%) had a UTI recurrence. The rate of recurrence was not statistically significantly different between the groups (p = 0.13).

The PRIVENT study included 576 patients with UTI [20]. Patients were allocated to two groups. Contrasting with previously cited RCTs, each group included patients with VUR and without VUR. Therefore, the study did not address VUR alone. One group received antibiotic prophylaxis and the other placebo. During the study period, UTI was diagnosed in 36 of 288 patients (13%) in the antibiotic group and in 55 of 288 (19%) in the placebo group, a difference of six percentage points (p = 0.029). The authors calculated that after 12 months, 14 patients would need to have been treated to prevent one UTI. In addition, when their data included only patients with VUR with or without prophylaxis the difference between the groups was not statistically different. Authors concluded that long-term, low-dose antibiotic use was associated with a modest reduction (seven percentage points) in the absolute risk of symptomatic urinary tract infection in children.

2. Does antibiotic prophylaxis prevent UTI in VUR patients? Since 2006, eight RCTs have been published comparing the rate of UTI recurrence between patients with reflux on or off long-term urinary antibiotic prophylaxis [14, 15, 19–24]. Although PRIVENT enrolled patients with or without VUR in the same group [19], the study has been included among the eight RCTs.

In these RCTs, the number of patients enrolled varied from 93 to 607. Placebo was used in three trials [14, 20, 24]. Among studies, patient population was rather heterogeneous regarding age, VUR grading, and methods of urine collection. In some of the RCTs, patients were enrolled after their first

febrile UTI. In other RCTs, patients had history of UTI(s) before enrollment.

In four of the five studies not using placebo, prophylactic antibiotics did not significantly reduce the recurrence rate in the prophylaxis group [15, 19, 21, 22]. In the Swedish trial [23], a beneficial effect of prophylaxis was observed but only in girls who made up 39% of the patients. This study is characterized by the high recurrence rate girls in the non-prophylaxis ("surveillance") group. This recurrence rate was much higher than the one observed in the other RCTs and in previously published data on Swedish children [28]. In addition, in this trial, the recurrences in 7 of the girls in the surveillance group did not meet bacteriological criteria for UTI, and in 10 patients, the sample technique was bag contrasting with only three in the prophylaxis group. These two features may have influenced the outcome results.

These studies were criticized because of small number of patients, the lack of placebo, no evaluation of bladder bowel dysfunction, and no data on adherence to antibiotic prophylaxis during the trial. However, in all of them, some of the criticism were softened by the use of bacteriological evidence of primary outcome (UTI) as objective criteria for UTI recurrence and by the fact that even in the studies including placebo, the compliance with the antibiotic was poor.

A meta-analysis of these studies in 2009 which did not include the Swedish trial (data not available for meta-analysis in 2009) did not demonstrate any advantage of using urinary antibiotic prophylaxis in cases of VUR grades II and III. Risk ratio of symptomatic urinary tract infection in the antibiotic group was 0.92 (range from 0.58 to 1.45) for grade III VUR and 0.90 (range from 0.42 to 1.90) for grade II [29].

There are two placebos, double-blind studies on the use of antibiotic prophylaxis in VUR patients. The RIVUR [14] enrolled 607 patients. At the end of 2 years of follow-up, recurrent urinary tract infection developed in 39 of 302 children who received prophylaxis (13%) as compared with 72 of 305 children who received placebo (24%). A difference of 33 children ($p < 0.001$). Authors estimated that a sample of 300 children in each study group would have provided at least 80% power to detect a reduction in the proportion of children with febrile or symptomatic recurrences during a 2-year follow-up period from 20% in the placebo group to 10% in the prophylaxis group. As shown on Fig. 3 of their report, the difference of > 10% was only observed at the end of the 2 years follow-up and decreased again to less than 10% a few months later. Moreover, authors found the 10% difference only in those patients younger than 2 years of age with VUR grade I–II ($p = 0.019$) but not in those with VUR grades III–IV ($p = 0.170$). This latter finding raises questions as to the use of routine antimicrobial prophylaxis in young children with VUR grades III and IV. Authors attributed the lack of beneficial effect in these groups to the small number of patients enrolled.

Boys represented only 8% of the children studied as compared with 33% of the 1660 children who participated in the previous six studies [30].

VCUG was obtained at 2 years in 428 children. Reflux had resolved in 218 children (50.9%), improved in 100 (23.4%), unchanged in 79 (18.5%), and worse in 31 (7.2%). Since it is not known when the VUR resolved, authors should have compared data only in children who had persistent VUR at the end of the 2 years.

Eight children would have had to be treated for 2 years to prevent one case of febrile or symptomatic urinary tract infection. However, according to Hewitt and Montini, "The treatment showed statistical, but not clinical, significance; 16 patient-years of antibiotics were required to prevent one urinary tract infection, and 22 patient-years of antibiotics were required to prevent one febrile urinary tract infection" [29].

Hari et al. in 2014 reported on 93 children (29 girls, 62 boys) age 1 to 12 years with VUR grades II to IV followed for 1 year [24]. During the study, at least one symptomatic UTI occurred in 10 of the 47(21.3%) patients receiving antibiotic prophylaxis and in three of the 46 (6.5%) patients receiving placebo (log rank test $p = 0.02$). Compared to the placebo group, the antibiotic group had a 14.8% absolute increase in the risk of UTI (95% CI 1–28, $p = 0.03$).

A recent meta-analysis on the role of antimicrobial prophylaxis in children with VUR included eight studies [31]. As previously mentioned, data from PRIVENT study were incorporated in the analysis. Unfortunately, authors did not include Hari study nor their input data for the Swedish study were correct. RIVUR [14] and PRIVENT [20] studies were graded as having a low risk of bias, and the remaining six studies [15, 19, 21–23] were considered to be at a high risk of performance and detection bias. The meta-analysis concluded that prophylaxis was effective in preventing recurrence of UTI even in those considered at high risk although, among them, only the Swedish study showed beneficial effect of prophylaxis.

An overview of the RCTs demonstrate variable subpopulations and methodologies of the studies evaluated. The many confounding effects suggest caution on recommendations or guidelines based on these meta-analyses.

3. Does urinary antibiotic prophylaxis decrease the rate of APN in VUR patients? There are only two studies on antibiotic prophylaxis and prevention of acute pyelonephritis in VUR patients. In a RCT open-labeled and unblinded that included 100 patients (30% of patients with grade IV VUR), Pennisi et al., after 2 years of follow-up, found that antibiotic prophylaxis was ineffective in preventing APN recurrences [15]. Unfortunately, patients were considered to have APN recurrence if they have a febrile UTI during the follow-up. In our study, involving 87 patients, each episode of recurrent APN was diagnosed on DMSA renal scan. Seven patients recurred in the

prophylaxis group and only one in the surveillance group ($p > 0.05$) [19].

4. Does urinary antibiotic prophylaxis prevent the development of renal scars? Renal scarring was a secondary endpoint for all trials. No significant difference in the prevention of new renal scars was noted after antimicrobial prophylaxis. None of the RCTS, including RIVUR, had been sufficiently powered to detect differences in the rates of scarring as a secondary outcome. Meta-analysis by Hewitt et al. in 2018 addressed this issue [32]. The analysis includes seven RCTs (1427 subjects) with six RCTs (1004 subjects) included in the subgroup meta-analysis restricted to those with VUR. All RCTs had renal scarring as a well-defined objective outcome. Both meta-analyses did not show differences in the incidence of scarring between the prophylaxis and no prophylaxis groups. New scarring was shown in 5.7% of all children and in 6.3% of those with VUR. There was no significant heterogeneity, and the funnel plots did not demonstrate evidence of publication bias.

Conclusions

A review of RCTs on VUR during the last 12 years allows us to revisit its clinical significance.

1. This review shows that the conventional assertions that VUR predispose to UTI, APN, and renal damage are not supported by the current data. (a) VUR does not lead to increase recurrence rate of UTI, especially in those with VUR grades I to III. Recurrences in grades IV and V seem to follow the same pattern although the evidence is not conclusive because of the small number of patients included in the studies. (b) The VUR as a risk for APN has not been confirmed but the limited available data suggest that VUR does no predispose to APN. Finally, (c) there is no evidence that VUR increases the incidence of renal scars in UTI patients with no dilating VUR. Available data on grades IV and V do not allow any conclusion, and new studies are needed to resolve this issue.
2. The assumption that antibiotic prophylaxis prevents UTI, APN, and renal parenchymal damage has not been confirmed. Some studies have shown a small benefit *from* antibiotic prophylaxis in preventing symptomatic and febrile UTIs. A mild statistically significant decrease in recurrence of UTI has been reported. However, the benefit is small since most of UTI patients do not relapse, and it is not known if those who frequently relapse would benefit from urinary antibiotic prophylaxis. There seems to be a consensus that children with normal urinary tracts or nondilating VUR do not benefit from prophylaxis.

There is a need to reassess our approach to VUR in children. Thus, it is necessary to design rigorous studies to identify the factors contributing to UTI recurrence, development of APN, and renal parenchymal scars in patients with or without reflux.

There are two issues that need to be addressed.

1. Will antibiotic prophylaxis benefit those patients with grades IV and V VUR? Except for the RIVUR study, there are no published data differentiating between non-dilating VUR and grade IV and V VUR. The RIVUR showed no beneficial effect in these patients although authors felt that the reason for the absence of benefit was that the study was not sufficiently powered.
2. Will antibiotic prophylaxis benefit those patients presenting frequent recurrences of UTI especially APN? No data are available to resolve these issues. Until the answers are provided, a cautious approach using prophylaxis in these clinical circumstances may be advocated.

The following conclusions can be inferred from this review:

1. It is not necessary to request a VCUG in every child with first febrile UTI unless abnormal RUS or other specific clinical circumstances are present. This is the approach of NICE and AAP and seems strongly supported by the review of available data. In addition, there is no need for routine VCUG in siblings of VUR patients unless they fulfill the criteria set by the AAP to request VCUG in case of febrile UTI.
2. It is not necessary to start routine antibiotic prophylaxis after a first febrile UTI in a VUR patient. The current thought is that antibiotic prophylaxis should be gear only to those patients considered to be at high risk for renal damage [33]. To avoid repeating past mistakes, rigorous studies are needed to define UTI patients that are at risk for renal damage and to assess the benefit of prophylaxis in those patients.
3. The use of long-term urinary antibiotic prophylaxis does have its drawbacks. The duration of follow-up during prophylaxis in reflux patients has not been defined. Increasing bacterial resistance and low adherence with prescribed medication represent major obstacles to try this mode of therapy.

The time to overinvestigate and treat the vast majority of otherwise healthy children who have an uncomplicated UTI with long-term antibiotic prophylaxis seems to come to an end. Is there a role of severe VUR in the development of chronic renal disease and renal failure? New ideas are needed to answer these questions. The responses will allow us to avoid repeating past mistakes when therapeutic choices were based on expert opinion rather than facts.

Study questions (answers appear following the reference list)

1. What percentage of VUR patients' siblings had no history of UTI?

   a) 20%
   b) 40%
   c) 75%

2. What is the estimated median years to resolution for grade IV VUR?

   a) 3.1 years
   b) 6.5 years
   c) 9.5
   d) 12.5

3. Do the RCTs reviewed above prove that VUR is a risk factor for

   a) UTI
   b) Acute pyelonephritis(APN)
   c) Renal parenchymal damage
   d) All of the above
   e) None of the above

4. In Hoberman' study, what percentage of children < 2 years of age with febrile UTI presented focal defects on DMSA scan compatible with acute pyelonephritis.

   a) 20%
   b) 50%
   c) 60%
   d) 75%

5. When urinary antibiotic prophylaxis could be started in VUR patients?

   a) After first febrile UTI.
   b) Never
   c) In patients with documented APN recurrences
   d) In patients presenting asymptomatic bacteriuria

Compliance with ethical standards

Conflict of interest The author has no conflict of interest to declare.

References

1. National Institute of Health and Clinical Excellence (NICE)(2007). Available at: www.nice.org.uk/CG54
2. American Academy Pediatrics Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB (2011) Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 128(595–610):13
3. Wan J, Skoog SJ, Hulbert WC, Casale AJ, Greenfield SP, Cheng EY, Peters CA, Executive Committee, Section on Urology, American Academy of Pediatrics (2012) Section on urology response to new guidelines for the diagnosis and management of UTI. Pediatrics 129:e1051–e1053
4. Tekgül S, Riedmiller H, Hoebeke P, Kočvara R, Nijman RJ, Radmayr C, Stein R, Dogan HS (2012) European Association of Urology EAU guidelines on vesicoureteral reflux in children. Eur Urol 62(3):534–542
5. Lee T, Ellimoottil C, Marchetti KA, Banerjee T, Ivančić V, Kraft KH, Bloom DA, Park JM, Wan J (2017) Impact of clinical guidelines on voiding Cystourethrogram use and vesicoureteral reflux incidence. https://doi.org/10.1016/j.juro.2017.08.099
6. Arant BS Jr (1991) Vesicoureteral reflux and renal injury. Am J Kidney Dis 17:491–511
7. Bailey RR (1979) In: Hodson CJ (ed) Kincaid SmithP reflux nephropathy, 1st edn. Masson, New York, pp 59–61
8. Noe HN (1992) The long-term results of prospective sibling reflux screening. J Urol 148:1739–1742
9. Murer L, Benetti E, Artifoni L (2007) Embryology and genetics of primary vesico-ureteric reflux and associated renal dysplasia. Pediatr Nephrol 22:788–797
10. Baker R, Maxted W, Maylath J, Shuman I (1966) Relation of age, sex and infection to reflux: data indicating high rate of spontaneous cure rate in pediatric patients. J Urol 95:27–32
11. Chand DH, Rhoades SA, Kraus S, Strife CF (2003) Incidence and severity of vesicoureteral reflux in children related to age, gender, race and diagnosis. J Urol 170:1548–1550
12. Arant BS Jr (1992) Medical management of mild and moderate vesicoureteral reflux: follow up studies of infants and young children. A preliminary report of the Southwest Pediatric Nephrology Study group. J Urol 148:1683–1687
13. Tamminem-Mobius T, Brunier E, Ebel KD, Lebowitz R, Olbing H, Seppanen U, Sixt R (1992) Cessation of vesicoureteral reflux for 5 years in infants and children allocated to medical treatment. J Urol 148:1662–1666
14. Trial Investigators RIVUR, Hoberman A, Greenfield SP, Mattoo TK, Keren R, Mathews R, Pohl HG, Kropp BP, Skoog SJ, Nelson CP, Moxey-Mims M, Chesney RW, Carpenter MA (2014) Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med 370:2367–2376
15. Pennesi M, Travan L, Peratoner L, Bordugo A, Cattaneo A, Ronfani L, Minisini S, Ventura A, North East Italy Prophylaxis in VUR study group (2008) Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. Pediatrics 121:e1489–e1494
16. Schwab WC Jr, Wu H-Y, Selman H, Smith GHH, Snyder HM, Canning DA (2002) Spontaneous resolution of vesicoureteral reflux: a 15-year perspective. J Urol 168:2594–2599
17. Kunin CM, Deutscher R, Paquin A Jr (1964) Urinary tract infection in school children: an epidemiological, clinical, and laboratory study. Medicine 43:91–130
18. Elo J, Tallgreen LG, Sarna S, Alfthan O, Stenstrom R (1981) The role of vesicoureteral reflux in pediatric urinary-tract infection. Scand J Urol Nephrol 15:243–248
19. Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos YL (2006) Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics 117(626–32):9

20. Craig JC, Simpson JM, Williams GJ, Lowe A, Reynolds GJ, McTaggart SJ, Hodson EM, Carapetis JR, Cranswick NE, Smith G, Irwig LM, Caldwell PH, Hamilton S, Roy LP (2009) Prevention of recurrent urinary tract infection in children with Vesicoureteric reflux and normal renal tracts (PRIVENT) antibiotic prophylaxis and recurrent urinary tract infection in children. N Engl J Med 361: 1748–1759
21. Montini G, Rigon L, Zucchetta P, Fregonese F, Toffolo A, Gobber D, Cecchin D, Pavanello L, Molinari PP, Maschio F, Zanchetta S, Cassar W, Casadio L, Crivellaro C, Fortunati P, Corsini A, Calderan A, Comacchio S, Tommasi L, Hewitt IK, Da Dalt L, Zacchello G, Dall'Amico R, IRIS Group (2008) Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, non-inferiority trial. Pediatrics 122:1064–1071
22. Roussey-Kesler G, Gadjos V, Idres N, Horen B, Ichay L, Leclair MD, Raymond F, Grellier A, Hazart I, de Parscau L, Salomon R, Champion G, Leroy V, Guigonis V, Siret D, Palcoux JB, Taque S, Lemoigne A, Nguyen JM, Guyot C (2008) 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 179:674–679
23. Brandström P, Esbjörner E, Herthelius M, Swerkersson S, Jodal U, Hansson S (2010) The Swedish reflux trial in children: III. Urinary tract infection pattern. J Urol 184:286–291
24. Hari P, Hari S, Sinha A, Kumar R, Kapil A, Pandey R, Bagga A (2015) Antibiotic prophylaxis in the management of vesicoureteric reflux: a randomized double-blind placebo-controlled trial. Pediatr Nephrol 30:479–486
25. Snodgrass WT, Shah A, Yang M, Kwon J, Villanueva C, Traylor J, Pritzker K, Nakonezny PA, Haley RW, Bush NC (2013) Prevalence and risk factors for renal scars in children with febrile UTI and/or VUR: a cross-sectional observational study of 565 consecutive patients. J Pediatr Urol 9:856–863
26. Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER (2003) Imaging studies after a first febrile urinary tract infection in young children. N Engl J Med 348:195–202
27. Hansson S, Jodal U, Norén L, Bjure J (1989) Untreated bacteriuria in asymptomatic girls with renal scarring. Pediatrics 84:964–968
28. Bergström T, Lincoln K, Redin B, Winberg J (1968) Studies of urinary tract infections in infancy and childhood. X. Short or long-term treatment in girls with first or second-time urinary tract infections uncomplicated by obstructive urological abnormalities. Acta Paediatr Scand 57:186–194
29. Hewitt I, Dall'Amico R, Montini G (2014) Letter to the editor. N Engl J Med 371:1070–1073
30. Montini G, Hewitt I (2009) Urinary tract infections: to prophylaxis or not to prophylaxis? Pediatr Nephrol 24:1605–1609
31. Wang HH, Gbadegesin RA, Foreman JW, Nagaraj SK, Wigfall DR, Wiener JS, Routh JC (2014) Efficacy of antibiotic prophylaxis in children with vesicoureteral reflux: systematic review and meta-analysis. J Urol 193:963–969
32. Hewitt IK, Pennesi M, Morello W, Ronfani L, Montini G (2017) Antibiotic prophylaxis for urinary tract infection-related renal scarring: a systematic review. Pediatrics. https://doi.org/10.1542/peds.2016-3145
33. Wang ZT, Wehbi E, Alam Y, Khoury A (2018) A reanalysis of the RIVUR trial using a risk classification system. J Urol 199:1608–1614

Answers

1. c; 2. c; 3. e; 4. c; 5. c