

Diagnostic Imaging after an Initial Febrile Urinary Tract Infection in Infants 2-24 Months Old: A Review of the Evidence

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Abstract

A Urinary Tract Infection (UTI) is an infection of the urinary system including the urethra, bladder, ureters, and kidneys. UTIs are typically caused by flora from the colon, most commonly *E. coli*. Infants typically present with non-specific symptoms of fever, poor feeding, and irritability, while older children may have more classic symptoms. Boys are more likely to develop a UTI in the first year of life, while after the first year they are more common in girls. In boys, circumcision decreases the risk of UTI at all ages. Overall 3-5% of girls experience a UTI, usually within the first 5 years of life.

Keywords: Diagnostic imaging; Pediatric; Urinary tract infection; Voiding cysto urethrogram

Introduction

In 2011, the American Academy of Pediatrics (AAP) released an updated clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants from 2-24 months. Of particular note, previous guidelines had included the routine use of a Voiding Cysto Urethro Gram (VCUG) in the diagnostic evaluation of infants after a febrile UTI. The new guidelines, however, recommend only targeted imaging with VCUG based on risk factors and recurrent infections [1-3] This change sparked controversy, and a debate regarding how to interpret the current literature and its implications for patient management [4,5].

What follows is a brief summary of the current clinical practice guidelines, a review of the controversy surrounding the recommendations regarding VCUG, and finally, a review of the literature related to the benefits of routine VCUG in a first-time febrile UTI in infants.

Summary of Current Guidelines

A total of 7 action statements are included in the updated clinical practice guidelines. The first two emphasize the importance of obtaining urine using a reliable method such as urine catheterization or Suprapubic Aspiration (SPA) prior to the initiation of antimicrobial therapy. Once obtained, a urine sample is considered diagnostic for a UTI if both the Urinalysis (UA) shows pyuria and/or bacteriuria, and culture shows $\geq 50,000$ Colony Forming Units (CFU) per mL. Once diagnosed, the guidelines recommend a 7-14 day course of antibiotics, with no preference for oral (PO) or Intravenous (IV) routes of administration based on local antimicrobial sensitivity patterns.

The guidelines state that all febrile infants diagnosed with a UTI should undergo renal and bladder ultrasonography (US) in the evaluation after an initial UTI. Unlike previous guidelines, VCUG is no longer recommended as routine following an initial, uncomplicated febrile UTI. But, if US show evidence of hydronephrosis, high grade Vesico-Ureteral Reflux (VUR), renal scarring, or obstructive uropathy, VCUG should then be considered. VCUG is also recommended in the case of recurrent febrile UTI. The guidelines suggest that VCUG can be considered if the first febrile UTI is atypical or complex, however no specific characteristics of an atypical UTI are enumerated. In all cases, prompt medical evaluation for future febrile illnesses to ensure prompt identification and treatment of recurrent UTI is emphasized [3,6].

Another change from previous guidelines is that repeat urine

cultures are no longer recommended after a urinary tract infection, recognizing the high rate of bacterial colonization in the urinary tract that does not represent infection.

Why is VCUG Questioned?

The goal of performing VCUG is to identify VUR, which has been thought to put patients at risk for recurrent upper urinary tract infections. This, in turn, was thought to put patients at risk for renal scarring and long-term renal complications. By treating these patients, clinicians have aimed to decrease long-term renal sequelae. For this approach to be effective there must be:

- (1) Increased identification of VUR by VCUG as compared to less invasive modalities such as US,
- (2) Reduced rate of recurrent UTI in patients treated with antibiotic prophylaxis,
- (3) Minimal additional risk conferred by chronic antibiotic treatment, and
- (4) Correlation between childhood UTI with development of renal scarring and Chronic Kidney Disease (CKD).

However, each of these statements has come into question. A review of the literature relevant to this debate follows.

Is VCUG Necessary to Identify VUR?

Tsai et al. [7] performed a prospective study of 220 infants <3 months old, presenting with a first febrile UTI. Each was screened with US, Dimercaptosuccinic acid (DMSA) scan, and VCUG. Analysis of their data showed 92% sensitivity of DMSA or US to identify high-grade reflux. They concluded that VCUG can be excluded from the workup if the less intrusive testing showed no abnormality. Current guidelines by the AAP, however, do not suggest the routine use of DMSA scanning.

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Reviewing their data for ultrasound alone, the sensitivity to identify high-grade reflux dropped to only 77%. With this finding, we can infer that applying the current clinical practice guidelines would result in a fairly low sensitivity to detect VUR. In applying this finding to clinical decisions, however, it is important to note that their study population only included young infants, and their findings may not be applicable to the entire 2-month through 2-year age group to which the AAP recommendations are focused.

Are prophylactic antibiotics effective at decreasing the rate of UTI?

Jodal et al. [8] compared treatment of high-grade reflux by randomly assigning patients <11 years old to either medical management with antibiotic prophylaxis or surgical management. Although that debate is beyond the scope of this review, some insight can be found in their data. The only statistically significant difference these researchers found was a higher rate of recurrent febrile UTI in the group treated medically. Although the age range is broader than our focus population, these findings suggest an increased risk for recurrent UTI in patients given long-term antibiotic prophylaxis for VUR.

Craig et al. [9] looked at this relationship more directly in their randomized placebo-controlled study comparing trimethoprim-sulfamethoxazole with placebo. Patients less than 18 years of age (median: 14 months) who had one or more urinary tract infections were randomized. 13% of patients in the treatment group were found to have recurrent febrile UTIs while 19% of the placebo group had UTI recurrence, a statistically significant difference. However, there was no difference in progression of renal scarring in the two groups. Moreover, treated patients had a higher rate of infection with resistant organisms. This constellation of findings calls into question whether the benefit outweighs the risk of long-term antibiotic prophylaxis. In applying their findings, though, one must note that they included patients who may have had multiple UTIs prior to enrollment; these children would fall into the group of patients which the current guidelines suggest are evaluated with VCUG. Also, although their study population does not match the age-range of the current practice guidelines since it includes patient through 18 years of age, the median age suggests that the majority of subjects were, in fact, <2 years old.

These findings are supported by a similar study done by Montini et al. [10] which included only children from 2 months to 7 years of age who presented with their first UTI. Their analysis for non-inferiority showed no statistical difference between treated and untreated groups in either rate of recurrent infection or progression of renal scarring.

Garin et al. [11] studied children 3 months to 18 years with a febrile UTI. Subjects were randomized into antibiotic prophylaxis versus no antibiotic prophylaxis. All patients in this study underwent VCUG, and presence of high-grade reflux (grade IV-V) was used as an exclusion criteria. Stratification was done to ensure that those with low-grade VUR and those without VUR were evenly distributed between study groups. They found no statistical difference in the rate of infection between those with low-grade reflux and no reflux. Similarly, there was no statistical difference between treated and untreated groups in terms of recurrent UTIs, or development of renal scars [12]. Although these results are compelling, those excluded from analysis (those with high-grade reflux) are those that are theoretically most at risk for recurrent infection, and those in which we should be most interested in seeing a difference from treatment with antibiotic prophylaxis.

Addressing this concern, Pennesi et al. [12] conducted a randomized-controlled trial assigning patients with grades II-IV reflux to either

receive antibiotic prophylaxis or not. Patients between 1 day and 30 months of life who presented with a first episode of febrile pyelonephritis were recruited. Intention-to-treat analysis was performed. Although their analysis revealed a tendency for increased rate of recurrence in prophylaxed patients, the difference was not statistically significant. There was also no statistical relationship between grade of reflux and rate of UTI recurrence. They did find a statistically significant difference in rate of drug-resistant UTIs, with the group receiving prophylaxis having a higher rate of drug-resistant infection. In terms of renal scar progression, there was no statistical difference in rate of progression for treated and untreated groups, and in no group was a new scar identified after 4-year follow up [13]. Their study group does include patients outside of the age-range of the current recommendations, but suggest a significant risk of multi-drug resistant UTIs in those treated with antibiotic prophylaxis without showing a clear long-term benefit.

Contrary to these findings, the Swedish Reflux Trial did identify a benefit of antibiotic prophylaxis, specifically in girls with grade III-IV VUR. DMSA scan was done prior to randomization of subjects in order to identify renal scarring. Overall, girls were more likely than boys to have recurrent UTIs. In girls, there was a statistical difference in recurrence, with those given antibiotic prophylaxis being less likely to have recurrent infection. In addition, the antibiotic prophylaxis group showed a statistically significant lower rate of scar progression. In boys, however, there was no statistically significant difference in either UTI recurrence or scar progression [14]. The results of this study suggest that a different approach to treating VUR might be warranted in girls and boys.

Are childhood urinary tract infections a risk factor for chronic kidney disease?

On review of the literature, Salo et al. [14] could find no documented cases for whom childhood UTIs were the main cause of chronic kidney disease. Subsequently chart review of all patients (n=366) treated with CKD at their institution revealed only 1 possible patient in whom childhood UTIs could be a possible explanation of CKD [15]. These authors concluded that childhood UTIs are not a significant risk factor for CKD in adulthood.

Looking at a case-series of 20 girls without scarring noted on DMSA after an initial UTI, but who did develop scarring after subsequent UTI, there was noted to be a statistically significant difference in time to treatment, with earlier treatment of UTI being associated with less scar progression [16]. Although this was a small group, and did not take into account VUR status, these results suggest that prompt identification and treatment of UTIs is protective against renal scarring.

What Would Happen if the Routine use of Vcug was Eliminated?

At Santa Clara Valley Medical Center, an institutional algorithm was put in place that limited the use of VCUG to patients with abnormal ultrasound, atypical UTIs, or recurrent UTIs, much as is suggested by the updated clinical practice guidelines. Schroeder et al. performed a retrospective chart review comparing outcomes before and after the initiation of this algorithm, looking at all children <2 years who presented with their first febrile UTI. They found no significant increase in rates of recurrent UTIs, but did show a substantial decrease in the use of antibiotics and frequency of VCUG [16].

A similar finding was reported by Pennesi et al. [17]. They retrospectively reviewed 406 children's records (1-36 months of age) who had presented with their first UTI. All had US done after their

first UTI, and a VCUG done if they had a recurrent UTI or abnormal US. 376 patients had normal renal US, of which 18 had recurrent UTI. Only 2 of those 18 had abnormal VCUG. They concluded that patients with febrile UTI and normal US do not require VCUG [17].

Summary

The current literature does not give us strong evidence that is specific to the 2-24 month age group regarding the role of VCUG after a first UTI. Extrapolating from studies done on subjects of a broader age range gives us some insight. US do not appear to be sufficient to identify VUR in all cases, with VCUG being more sensitive than US alone. However, once identified, it is unclear as to whether prophylactic antibiotics are useful in preventing recurrent infections in patients with VUR. There may be a small decrease in recurrent UTIs, but with that benefit comes an increased risk of subsequent infections being attributed to multi-drug resistant organisms. Prompt identification and treatment for recurrent infections in these cases may be as protective against renal scar progression. As such, it is unclear as to whether routine use of prophylaxis is warranted. It follows that the benefit of identifying VUR with VCUG is unclear.

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