Controversy in Urinary Tract Infection Management in Children: A Review of New Data and Subsequent Changes in Guidelines

by Jameela Abdulaziz Kari,1,2 and Kjell Tullus1

1Department of Pediatrics, Faculty of Medicine, King Abdulaziz University, Saudi Arabia
2Department of Nephrology, Great Ormond Street Hospital for Children, UK

Correspondence: Jameela A. Kari, Department of Pediatrics, King Abdulaziz University Hospital, PO Box 80215, Jeddah 21589, Saudi Arabia. Telephone: +996 55677904. Fax: +996 (2) 6684603. E-mail <jkari@doctors.org.uk>.

Summary

Controversy and lack of consensus have been encountered in the management of pediatric urinary tract infection (UTI), including its diagnosis, radiological investigations and the use of antibiotic therapy. In this review, we discuss the need for radiological investigations and the extent of their use as well as the need for prophylactic antibiotics in children with UTI and vesicoureteral reflux. Only a small proportion of children with first UTI and no history of antenatal renal abnormalities have clinically important malformations. Renal ultrasound should be performed in febrile infants and young children with UTI; a micturating cystourethrogram should not be performed routinely after the first febrile UTI. Long-term antibiotics appear to reduce the risk of recurrent symptomatic UTI in susceptible children, although the clinical benefit is marginal. Current recommendations encourage performing radiological investigations only in children at risk and discourage routine prophylactic antibiotic use.

Key words: children, radiological investigations, urinary tract infection, vesicoureteral reflux

Introduction

Imaging tests have been traditionally performed in pediatric patients with urinary tract infection (UTI) with the aim of detecting renal anomalies and vesicoureteral reflux (VUR). It was thought that the detection of VUR would give an opportunity for physicians to intervene early, either by treating the VUR surgically or by using prophylactic antibiotics, to prevent subsequent renal scarring.

Formerly, the American Academy of Pediatrics (AAP) [1] and the Royal College of Physicians of London [2] recommended that infants and young children with first-time UTI should have imaging tests to evaluate the possibility of VUR. The severity of VUR was thought to correlate with the risk of developing permanent renal scarring. It was also believed that this scarring would cause serious sequelae later in life, such as hypertension, pregnancy complications, renal failure and, even, end-stage renal disease (ESRD). Those recommendations resulted from earlier studies that showed that renal scarring was present in 10–25% and VUR was present in 30% of children with UTI [3–5]. It has, however, recently become increasingly evident that these previous approaches led to overdiagnosis and overtreatment of clinically insignificant VUR.

The new recommendations from the AAP and the National Institute for Health and Clinical Excellence (NICE) in the UK state that radiological
investigations should be markedly reduced in children with UTI [6, 7].

In the current review, we discuss the new data about the need for radiological investigations and the extent of their use as well as the need for prophylactic antibiotics in children with UTI and VUR to prevent further UTI. We also discuss changes in the guidelines for radiological investigations and present NICE and AAP guidelines in detail.

**Why Should We Reduce the Radiological Investigations in Children With UTI?**

The aim of investigating children with UTI is to prevent long-term complications that were thought to be the result of renal scars known to develop as sequelae to the infection. However, during the past decade, there have been several important studies that have questioned this understanding. There is evidence that renal scars often are congenital or primary, with *in utero* renal damage, particularly in boys, where they are usually associated with dilated reflux [8, 9]. The severity of renal scars seen post UTI and subsequent impairment of kidney function has come into question. We have learnt that most significant renal anomalies are detected antenatally during the performance of routine ultrasound in the mothers [10]. Therefore, in children with first UTI and history of normal urinary tract ultrasound antenatally, clinically important malformations are only found in a small percentage.

Several recent studies have also questioned the need to explore the possibility of VUR in all children with a single episode of acute pyelonephritis. There is evidence that early diagnosis and early treatment are more important than prophylaxis in preventing renal scars [9]. Fernandez-Menendez et al. [11] reported that a therapeutic delay time of 48 hours or more was associated with renal scars in children with UTI. They also observed that children with abnormal renal scans had longer mean therapeutic delay time than those with normal scans ($p < 0.0005$). In another study on 20 girls with UTI and VUR, Coulthard et al. [12] reported that prompt treatment appeared to prevent scarring in children with VUR.

We will here review the data that underlie the shift in policy and also give recommendations on how to manage a child with febrile UTI.

**The Importance of Postinfectious Renal Scars**

It is obvious in pediatric nephrology practice that severe impairment of kidney function in children is related to dysplastic or scarred kidneys. The important question is how common that is after a first episode of febrile UTI. To understand this, one will need to review population-based epidemiological studies. Several such studies have been done in the city, Gothenburg (500,000 inhabitants). We present data from this important series of studies.

All children in Gothenburg who had an episode of UTI were followed by Wennerstrom et al. [13] for a mean of 17 years. They demonstrated that the glomerular filtration rate was well-preserved in all children with unilateral or no renal scarring, whereas a few children with bilateral scarring showed some degree of impairment of their renal function [13]. They performed 24-hour blood pressure recordings in all children with scars. The blood pressure curves were identical in children with and without scars. They also reported a low risk of hypertension 2 decades after childhood UTI, with mean systolic or diastolic blood pressure above $+2$ SD in 9% of the patients in the scarring group and in 6% of those in the non-scarring group [14].

In this context, it is useful to consider new patient data that were obtained from the Australia and New Zealand Dialysis and Transplant Registry [15], collected between the years 1972 and 1988, when the policy of optimum treatment of VUR was adopted. These data show that intensive investigation and treatment of children with febrile UTI has not been accompanied by the expected reduction in the incidence of ESRD attributable to reflux nephropathy [15].

**The Importance of VUR**

It is well-known that significant VUR is associated with recurrent febrile UTI, which can result in renal scarring [6, 16]. This is particularly true for higher-grade VUR, grade III or IV. On the other hand, acute lesions of a clinically notable size may develop even in the absence of VUR [17]. Significant VUR is usually associated with abnormal bladder function and initial abnormal renal scans [18]. It is therefore understandable that a lot of emphasis was laid on the detection and treatment of VUR in childhood. This is because it was believed that ESRD attributable to reflux nephropathy was preventable by the active treatment of children with VUR, with long-term antibiotics and ureteric reimplantation surgery.

However, it is noteworthy that several major developments have changed this approach. Over the past 6 years, important studies have evaluated the impact of long-term antibiotics on the recurrence rate of febrile UTIs and on the development of renal scars [6]. Studies have also investigated whether surgical treatment of VUR reduced subsequent renal scarring. Such studies have inferred that the clinical benefit of these surgical interventions is marginal [19].

Population studies have shown that in a large majority of cases, VUR depletes away with the passage of time. This can take quite many years, but after a 10-year follow-up, VUR was persistent in only a small minority of children [20].
Prophylactic Antibiotics for Preventing Recurrent UTI in Children

Prophylactic antibiotics have been used by most pediatricians as a routine measure in children with VUR. However, recent evidence concludes that prophylaxis should not be routinely recommended. In the recent AAP clinical practice guidelines, they performed a meta-analysis of the raw data of six most recent randomized controlled clinical trials (RCTs) involving 1091 infants (2–24 months of age). The result of this meta-analysis did not support the use of antimicrobial prophylaxis to prevent febrile recurrent UTI in infants without VUR or with grade I–IV VUR. Only five infants with grade-V VUR were included in the RCTs; therefore, no conclusion could be drawn in that group [6]. Similarly, the Cochrane group reviewed 12 RCTs (involving 1557 children), with six comparing antibiotics with placebo/no treatment. When all studies were included, antibiotics did not appear to reduce the risk of symptomatic UTI. However, when they evaluated the effects of antibiotics only in studies with low risk of bias, there was a statistically significant reduction in UTI. The Cochrane group concluded that long-term antibiotics appeared to reduce the risk of repeat symptomatic UTI in susceptible children, but the benefit was small and must be considered together with the increased risk of microbial resistance [21].

Treatment or prophylaxis is unnecessary in children with asymptomatic bacteriuria [22].

Surgery for VUR to Prevent Renal Scarring

A large European reflux study randomized children with grade-III and -IV VUR to either have their reflux surgically corrected or have treatment with prophylactic antibiotics. No differences were found between the two groups in the proportion of children who had developed new renal scars, neither at the 5- nor at the 10-year follow-up [23]. In a study from Great Ormond Street Hospital for Children, the authors assessed the kidney function by measuring the glomerular filtration rate of children treated with surgery or antibiotics for 10 years, and similarly, no difference was found between the two groups [24]. Prophylactic antibiotics were reported to prevent recurrent febrile UTIs and new renal damage in girls with dilated VUR, in a well-designed Swedish study that compared surgery, prophylactic antibiotics and surveillance in children with VUR [25].

Which Investigations Should Be Done?

The current recommended diagnostic strategies tend to minimize the number of unnecessary investigations, preferring those that are less invasive and that expose children to the smallest radiological risk. As the target of therapy is the prevention of parenchymal damage and not the detection of clinically insignificant VUR (non-dilated ureters, normal bladder function and normal initial renal scans), we should focus investigations on children at risk of having major or significant malformations. This includes children with recurrent UTI or any of the following atypical UTI presentations, according to NICE guidelines [7]:

1. Impaired urine flow
2. Palpable mass in the abdomen
3. Serious septic presentation
4. Bacteremia
5. Increased serum creatinine
6. Slow response to treatment—no notable improvement within 48 hours
7. Infection with a non-<i>Escherichia coli</i> bacteria
8. Any prenatal urinary tract finding

The NICE recommends that for infants younger than 6 months with the first UTI and without atypical features, only renal ultrasound is recommended within 6 weeks [7]. Only those with recurrent UTI or atypical UTI should have renal ultrasound during acute infection as well as micturating cystourethrogram (MCUG) and Tc-99 m dimercaptosuccinic acid (DMSA) 4–6 months after acute infection (Table 1) [7]. Similarly, the AAP guidelines recommend that febrile infants and young children (2–24 months) with UTIs should undergo renal and bladder ultrasound (evidence quality: C; recommendation) [6]. They recommend also that MCUG should not be performed routinely after the first febrile UTI; MCUG is indicated if ultrasound reveals hydronephrosis, scarring or other findings that would suggest either high-grade VUR or obstructive uropathy as well as any other atypical or complex clinical circumstances (evidence quality: B; recommendation) (Table 2).

The AAP also recommends further evaluation for recurrent febrile UTI (Table 2) [6]. The NICE recommends fewer investigations for young children aged 6 months to 3 years (Table 1) [7]. For the first UTI with no atypical feature, no investigations are recommended. Ultrasound during acute infection is recommended only for children with atypical UTI, and it should be performed within 6 weeks for those with recurrent UTI. In both cases, it is necessary to perform a DMSA scan 4–6 months after acute infection [7]. For children aged 3 years or older, the NICE recommends ultrasound during the infection only if the children presented with atypical UTI, whereas in those with straightforward presentation, no radiological investigations are required. For children with recurrent UTI, ultrasound within 6 weeks is required, followed by DMSA scan 4–6 months after acute infection (Table 1).

The results of antenatal screening play an important role in deciding investigations for UTI. If antenatal ultrasound is to be relied on when choosing post-UTI investigations, it is vital that it is performed...
TABLE 1
NICE recommendation for imaging schedule for infants and children

<table>
<thead>
<tr>
<th>Test</th>
<th>Respond well</th>
<th>Severe clinical illness or no response</th>
<th>Recurrent UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>US during the acute infection</td>
<td>No</td>
<td>Yes</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>US within 6 weeks</td>
<td>Only for infants &lt;6 months</td>
<td>No</td>
<td>For children up to 3 years old</td>
</tr>
<tr>
<td>DMSA 4-6 months after acute infection</td>
<td>No</td>
<td>Only for infants &lt;6 months</td>
<td>Yes</td>
</tr>
<tr>
<td>MCUG</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DMSA, dimercaptosuccinic acid; MCUG, micturating cystourethrogram; NICE, National Institute for Health and Clinical Excellence; US, ultrasound; UTI, urinary tract infection.

aData adapted from the National Institute for Health and Clinical Excellence [7].

TABLE 2
AAP recommendation for imaging schedule for infants (2–24 months)

<table>
<thead>
<tr>
<th>Test</th>
<th>Respond well</th>
<th>Severe clinical illness or no response</th>
<th>Recurrent UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>US during the acute infection</td>
<td>No</td>
<td>Yes</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>US later on MCUG</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

AAP, American Academy of Pediatrics; MCUG, micturating cystourethrogram; US, ultrasound; UTI, urinary tract infection.

in a structured and reliable manner, as an organ screening/malformation screening program in all children in the population. Unfortunately, this is not the case in most countries, in the developing as well as in the developed parts of the globe.

DMSA scan is recommended, as it can be used to detect children with risk of having dilated VUR [26]. Normal DMSA of both kidneys is associated with early resolution of VUR in infants and normal bladder function in the majority of them, whereas abnormal kidneys are associated with severe VUR and abnormal bladder function. Therefore, abnormal renal scans are an important independent predictor of early failure to resolve VUR [27], whereas a normal DMSA scan makes MCUG unnecessary in the primary examination of infants with UTI [28].

**Bowel Bladder Dysfunction**

Voiding dysfunction and chronic functional constipation could be the underlying causes of recurrent UTI, without congenital or anatomical abnormalities [29, 30]. Abnormal bladder pressure and urinary stasis predispose these children to developing recurrent UTI. Proper evaluation and management is mandatory to prevent UTI and damage to the kidneys.

**Conclusion**

(i) The evaluation of UTIs should focus on renal status rather than presence or absence of VUR.

(ii) Focus radiological investigations on children at risk (recurrent UTI or atypical presentation).

(iii) MCUG is indicated in patients with positive DMSA scan or recurrent febrile UTI. With this approach, MCUGs will be avoided in up to 50% of the children.

(iv) More investigations might be justified in developing countries with a higher risk of diagnostic delay and fewer prenatal ultrasound scans.

(v) Do not use antibiotic prophylaxis routinely.

(vi) Overinvestigation of low-risk patients and overtreatment of clinically insignificant VUR will be avoided when new guidelines are followed.

**References**


