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Avoidance of voiding cystourethrography in infants younger than 3 months with *Escherichia coli* urinary tract infection and normal renal ultrasound

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ABSTRACT

Background and objective Urinary tract infection (UTI) represents the most common bacterial infection in infants, and its prevalence increases with the presence of high-grade vesicoureteral reflux (VUR). However, voiding cystourethrography (VCUG) is invasive, and its indication in infants <3 months is not yet defined. This study aims to investigate, in infants aged 0–3 months, if the presence of *Escherichia coli* versus non-*E. coli* bacteria and/or normal or abnormal renal ultrasound (US) could avoid the use of VCUG.

Method One hundred and twenty-two infants with a first febrile UTI were enrolled. High-grade VUR was defined by the presence of VUR grade ≥III. The presence of high-grade VUR was recorded using VCUG, and correlated with the presence of *E. coli*/non-*E. coli* UTI and with the presence of normal/abnormal renal US. The Bayes theorem was used to calculate pretest and post-test probability.

Results The probability of high-grade VUR was 3% in the presence of urinary *E. coli* infection. Adding a normal renal US finding decreased this probability to 1%. However, in the presence of non-*E. coli* bacteria, the probability of high-grade VUR was 26%, and adding an abnormal US finding increased further this probability to 55%.

Conclusions In infants aged 0–3 months with a first febrile UTI, the presence of *E. coli* and normal renal US findings allow to safely avoid VCUG. Performing VCUG only in infants with UTI secondary to non-*E. coli* bacteria and/or abnormal US would save many unnecessary invasive procedures, limit radiation exposure, with a very low risk (<1%) of missing a high-grade VUR.

What is already known on this topic?

- Urinary tract infection (UTI) represents the most common bacterial infection in infants. It is frequently associated with anatomical urinary tract abnormalities such as vesicoureteral reflux.
- Voiding cystourethrography (VCUG) represents the gold standard method to diagnose vesicoureteral reflux; however, the VCUG is an invasive procedure.
- The indication of VCUG in infants below the age of 3 months, after the first UTI, is not yet defined and clinicians referred to their medical society recommendations.

What this study adds?

- In infants aged 0–3 months with a first urinary infection, the presence of *Escherichia coli* and normal renal ultrasound (US) findings allow to safely avoid VCUG.
- This novel approach based on the characterisation of bacterial species and the renal US findings would save unnecessary invasive procedures, with a low risk of missing a high-grade vesicoureteral reflux.

INTRODUCTION

Urinary tract infection (UTI) represents the most common bacterial infection in infants with a prevalence of 4.6% to 7.5%.[1] In this age group, UTI is frequently associated with anatomical urinary tract abnormalities such as vesicoureteral reflux (VUR). Voiding cystourethrography (VCUG) represents the gold standard method to diagnose VUR; however, the VCUG is an invasive procedure, with significant radiation exposure, and its indication in infants below the age of 3 months, after a first febrile UTI, is not yet defined. In such situations, clinicians follow their medical society recommendations.[2–8] The British and American guidelines recommend a VCUG in all infants with abnormal renal ultrasound (US) and/or in case of atypical or recurrent UTI, below the age of 6 months and between 2 and 24 months, respectively.[2 3] In Switzerland, the Swiss Society of Paediatrics recommends to perform a renal US and a VCUG in all children under the age of 3 months after the first UTI.[8] Finally, the Italian and French guidelines recommend a VCUG in all infants with an abnormal renal US (table 1).[4 5] However, high-grade VUR affects only 10% of infants with a first febrile UTI and then, applying these recommendations universally to all age groups would lead to many unnecessary investigations.

To our knowledge, there is no study investigating the association between the presence of both urinary non-*E. coli* bacterial infection and renal US findings in predicting high-grade VUR in infants below 3 months of age. In this study, we aimed to investigate, in infants below 3 months with a first febrile UTI, if the presence of urinary *E. coli* versus non-*E. coli* bacteria and/or normal or abnormal renal US could avoid the use of VCUG.

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Table 1 Recommendations regarding uroradiological imaging in children with UTI

	NICE[3 6] <6 months	AAP[2] 2–24 months	Italy[4] 2–36 months	Switzerland[8] 0–16 years	France[5] 0–16 years
Renal US	All*	All†	- Atypical or recurrent UTI - Male infants <6 months	All†	All†
VCUG	- Abnormal renal US - Atypical or recurrent UTI	- Abnormal renal US - Atypical or recurrent UTI - Complex clinical circumstances	- Abnormal renal US	- Abnormal renal US - ≤3 months - Recurrent UTI - Family history of VUR	- Abnormal renal US - Bladder dysfunction in male

*In case of atypical/recurrent UTI or UTI not responding to treatment, renal US should be performed during the acute phase.
†Renal US should be performed during the acute phase.
Atypical as defined by NICE recommendations: poor urine flow, septicaemia, abdominal mass, raised creatinine levels, non-E. coli bacteria, failure to respond to treatment within 48 hours. Recurrent UTI: two or more episodes of UTI.
AAP, American Academy of Pediatrics; NICE, National Institute for Health and Care Excellence; US, ultrasound; UTI, urinary tract infection, VUR, vesicoureteral reflux.

PATIENTS AND METHODS

All medical charts of infants <3 months of age with a first febrile UTI admitted to our tertiary centre between January 2009 and December 2014 were retrieved via our coding system. The study was approved by the local ethics committee (number 74/14). Inclusion criteria were as follows: fever ≥38°, a first UTI confirmed by urine culture obtained via bladder catheterisation or suprapubic aspiration, and the completion of a renal US (1–6 days from admission) and a VCUG (2–8 weeks after UTI). Positive urine culture was defined as a growth of a single microorganism $\geq 10^5$ colony-forming units (CFU) per mL with bladder catheterisation, or any growth by suprapubic puncture.[9] Patients with known abnormalities of the kidney or/and urinary tract were excluded.

Renal US was performed by trained paediatric radiologists and abnormal renal US was defined by renal pelvic anteroposterior diameter ≥5 mm, and/or any grade of dilatation of calyces or ureters, and/or pelvic or ureteral wall thickening.[10] VUR was graded according to the International Reflux Study Committee classification and high-grade VUR was defined as VUR grade III, IV or V.[11] In children with bilateral VUR, the higher grade of VUR was recorded.

Statistical analysis

Statistics were performed using the statistical software Epi-Info V.3.5.4 (Centres for Disease Control and Prevention). The χ^2 or Fischer exact test was used to compare proportion between groups as appropriate. Sensitivity, specificity, positive and negative likelihood ratio (PLR, NLR), diagnostic odd ratio (DOR) and corresponding 95% CI were calculated. Bayes theorem was used to calculate pretest and post-test probability for diagnostic algorithm.

RESULTS

One hundred and thirty-four infants were admitted to our hospital with a diagnosis of febrile UTI. One, five and six patients did not undergo renal US, VCUG or both examinations, respectively, and were therefore excluded. One hundred and twenty-two infants were enrolled. Mean age (±SD) at the time of febrile UTI was 43±25 days. There were 97 (79.5%) boys and 25 (20.5%) girls. Urine culture growth *E. coli* in 72% of cases. *Enterococcus faecalis*, *Klebsiella pneumonia* and other bacteria caused 10%, 10% and 8% of all febrile UTI, respectively (table 2). Normal renal US and normal VCUG were found in 82% and 80% of patients, respectively. Three per cent of infants had VUR grade I, 7% had grade II and 10% had high-grade VUR (III, IV and V) (table 3). Renal US was normal in 4, and abnormal in 8 out of 12 patients with high-grade VUR. The mean (SD) and range of ureteral and pelvic dilatation in patients with VUR grade ≥ III are 5.5±2.1 mm (3–7.8 mm) and 7.7±4.4 mm (3–20 mm), respectively. Neither gender (10% for boys vs 8% for girls, p>0.1) nor age (below 1 month vs between 1 and 3 months) was associated with high-grade VUR (table 4).

Results also showed that non-*E. coli* urinary infection and abnormal renal US were significantly associated with high-grade VUR (p<0.001) (table 4). The presence of urinary non-*E. coli* infection alone was able to predict a high-grade VUR with a sensitivity of 75% (95% CI 51% to 100%) and a specificity of 77% (95% CI 69% to 85%). The PLR was 3.3 (95% CI 0.8 to 13), the NLR was 0.3 (95% CI 0.08 to 1.3) and the DOR was 10 (95% CI 2.6 to 41) (table 5). Furthermore, the presence of abnormal renal US alone could predict the presence of high-grade VUR with a sensitivity of 58% (95% CI 30% to 86%) and a specificity of 86% (95% CI 80% to 93%). The PLR was 4.3 (95% CI 1.2 to 15), the NLR was 0.48 (95% CI 0.14 to 1.8) and the DOR was 8.9 (95% CI 2.5 to 31). Adding abnormal US findings in the group with non-*E. coli* infection improved the probability of detecting high-grade VUR from 26% to 55% with a DOR of 6.7 (95% CI 1.2 to 33). In addition, adding abnormal US findings in the group with *E. coli* infection improved the probability of detecting high-grade VUR from 3% to 15% with a DOR of 13 (95% CI 1.1 to 161) (table 5).

On the other hand, the presence of a normal renal US decreases the probability of having a high-grade VUR to 1% in children with an *E. coli* UTI. Similarly, the presence of a normal renal US decreases the probability of having a high-grade VUR to 15% in children with a non-*E. coli* UTI (figure 1).

All infants with high-grade VUR received uroprophylaxis for at least 2 years. During the follow-up of these 12 infants, five patients presented recurrent pyelonephritis. In addition, five infants had renal hypodysplasia on the refluxing side. None of them were known to have a renal hypodysplasia on the refluxing

Table 2 Bacterial urine culture results

	n=122	Per cent
Escherichia coli	88	72
Enterococcus faecalis	12	10
Klebseila pneumoniae	12	10
Klebseila oxytoca	4	3.3
Proteus mirabilis	2	1.6
Streptocoque B	1	1.6
Streptococcus alpha	1	0.8
Pyocyanic	1	0.8
Enterobacter cloacae	1	0.8

Table 3 Voiding cystourethrography (VCUG) findings

	n=122	Per cent
VCUG		
Normal	97	80
VUR grade I	4	3
VUR grade II	9	7
VUR grade III	5	4
VUR grade IV	5	4
VUR grade V	2	2

n, total number of patients; VUR, vesicoureteral reflux.

side before documented UTI. Seven patients required surgical intervention (Cohen procedure) for breakthrough UTI, including the five patients with renal hypodysplasia.

DISCUSSION

This study showed that infants younger than 3 months of age with a first febrile UTI secondary to non-*E. coli* bacteria have a 10 time increased risk of high-grade VUR compared with infants with *E. coli* infection. The association between non-*E. coli* UTI and urological malformations has been previously reported. Friedman *et al*[12] showed in children aged 1 week to 6 years with pyelonephritis, a significant association (DOR ≥8) between a non-*E. coli* UTI and the presence of urinary tract anomalies, for example, VUR grades III–IV, hydronephrosis and/or ureteropelvic junction obstruction. Moreover, Honkinen *et al*[13] found in a retrospective study that the probability of high-grade VUR (IV– V) was multiplied by 2.6 when the first UTI was caused by *Klebsiella pneumoniae*, *Enterococcus faecalis* or *Proteus mirabilis*. Finally, Jantunen *et al*[14] also showed in infants aged 1–24 months with a non-*E. coli* UTI a significant relative risk (3.4, 95% CI 2.2 to 5.3) of urinary tract abnormalities (VUR grades III–IV and hydronephrosis).

Several studies analysed the role of renal US in predicting high-grade VUR with conflicting results and with a various percentage of sensitivity and specificity.[15–18] Recently, Hung *et al*[15] and Ismaili *et al*[16 19] showed that renal US can efficiently predict high-grade VUR with a sensitivity of 64% to 70% and a specificity of 77% to 89%. However, Kaneko *et al*[17] showed that avoiding VCUG after the first febrile UTI, in infants aged below 3 months with normal renal US findings, would have resulted in missing 35.7% of high-grade VUR.

Table 4 Risk factors for high-grade VUR after the first urinary tract infection, according to the gender, age, urinary pathogen species and renal US findings

	High-grade VUR Total=12 n (%)	Non-high-grade VUR Total=110 n (%)	p
Gender			
Boys	10 (10)	87 (90)	0.39
Girls	2 (8)	23 (92)	
Age			
Less than 1 month	5 (11)	39 (89)	0.5
Between 1 and 3 months	7 (9)	71 (91)	
Pathogen			
E. coli	3 (3)	85 (97)	<0.01
Non *E. coli*	9 (26)	25 (73)	
Renal US			
Normal	5 (5)	95 (95)	<0.01
Abnormal	7 (31)	15 (68)	

E. coli, Escherichia coli; n, total number of patients; VCUG, voiding cystourethrography; VUR, vesicoureteral reflux; US, ultrasound.

Table 5 Determinant of high-grade vesicoureteral reflux in infants after a first febrile UTI

	Sensitivity (%) 95% CI	Specificity (%) 95% CI	PLR 95% CI	NLR 95% CI	DOR 95% CI
Non *E. coli*	75 51 to 1	77 69 to 85	3.3 0.8 to 13	0.3 0.08 to 1.3	10 2.6 to 41
Abnormal renal US	58 30 to 86	86 80 to 93	4.3 1.2 to 15	0.48 0.14 to 1.8	8.9 2.5 to 31
Abnormal renal US and non-*E. coli* UTI	56 23 to 88	84 70 to 98	3.5 0.6 to 19	0.5 0.1 to 3	6.7 1.2 to 33
Abnormal renal US and *E. coli* UTI	67 13 to 100	87 80 to 94	5.1 0.43 to 61	0.38 0.03 to 4.5	13 1.1 to 161

DOR, diagnostic OR; E. coli, Escherichia coli; n, total number of patients; NLR, negative likelihood ratio; PLR, positive likelihood ratio; US, ultrasound; UTI, urinary tract infection.

To our knowledge, no study investigated the value of renal US in children with non-*E. coli* UTI in detecting high-grade VUR. This study is the first to demonstrate that the addition of abnormal US findings to this group of infants with non-*E. coli* infection increases the probability to predict high-grade VUR from 26% to 55% with a DOR of 6.7.

Based on these results, we propose a probabilistic diagnostic algorithm. This novel approach is based on the characterisation of bacterial species causing UTI and the renal US findings. In this algorithm, the presence of *E. coli* UTI associated with a normal renal US reduces the probability of high-grade VUR to <1% (1/122) and then allow to safely avoid unnecessary VCUG in this group. Following this algorithm, the indication of VCUG can be limited to infants with non-*E. coli* UTI and/or abnormal renal US. This could reduce the indications of VCUG in 62% (75/122) of infant below the age of 3 months, and would save many unnecessary invasive procedures, limit radiation exposure, with a very low risk (<1%) to miss a high-grade VUR. Some clinicians define high grade VUR as VUR grade IV and V. When considering this last definition and in reference to figure 1, there was no single patient displaying a high grade VUR (IV or V) in the presence of an *E. coli* UTI associated with a normal renal US. In addition, 4 out of the 5 detected VUR in the group with a non-*E. coli* UTI associated with an abnormal renal US were of high grade (IV or V). These results strengthen the current National Institute for Health and Care Excellence guidelines regarding imaging tests in children with UTI and extend the American Academy of Pediatrics recommendations to infants aged <2 months.[3 6]

This study has several limitations. First, boys are over-represented (79%) in our cohort, which correlates with other studies in this field.[14 18 20–22] Therefore, the generalisability of the proposed algorithm needs to be assessed in girls. However, we found no association between gender and the presence of a high-grade VUR (10% in boys vs 8% in girls), confirming the findings of Jantunen *et al*[14] Circumcision status was not recorded. However, the indications for such procedure in our centre are very limited. Second, we have adopted a fairly strict definition of a positive urinary bacterial growth (≥10^5 CFU per mL using bladder catheterisation). Some clinicians

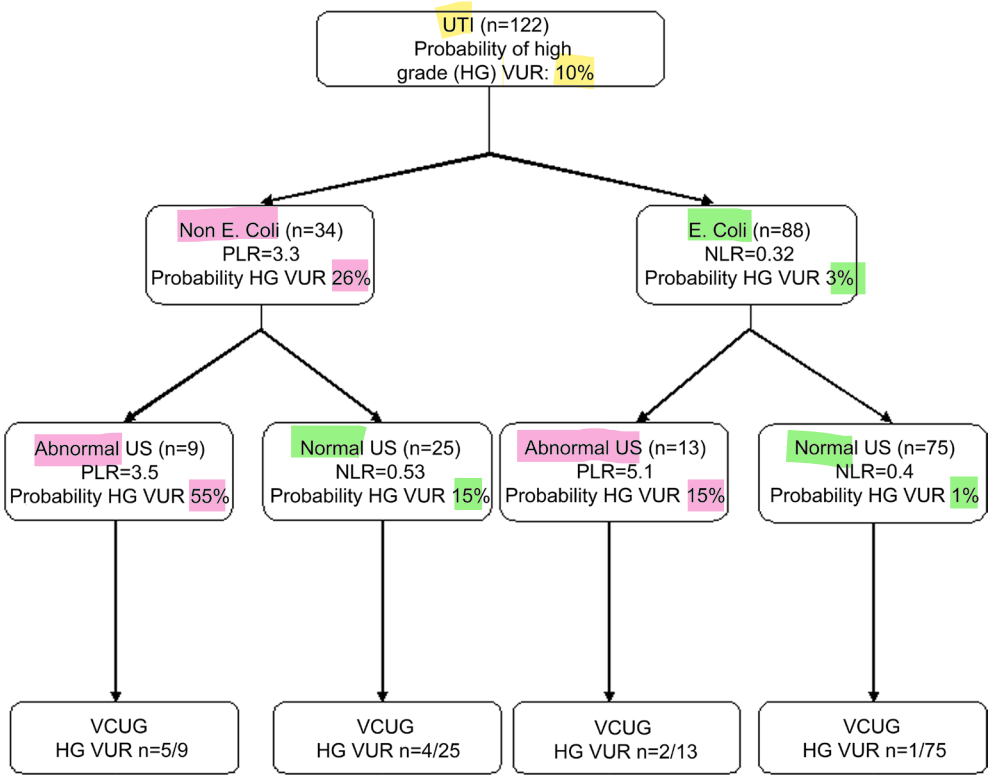

Figure 1 Probabilistic diagnostic algorithm for high-grade vesicoureteral reflux (≥III) in infants aged ≤3 months with first febrile UTI. *E. coli*, *Escherichia coli*; HG VUR, high-grade vesicoureteral reflux; NLR, negative likelihood ratio; PLR, positive likelihood ratio; US, renal ultrasound; UTI, urinary tract infection; VCUG, voiding cystourethrography.

consider a positive urine bacterial culture $<10^5$ CFU per mL. Therefore, we cannot rule out a bias in our results due to the inclusion of more severe cases. Third, given the small number of patients in the group with a non-*E. coli* UTI associated with a normal renal US and in the group with an *E. coli* UTI associated with an abnormal renal US, the indication of VCUG may be discussed and a large prospective study should be performed. Finally, breakthrough UTI might also result from acquired resistance to the antibiotic used for prophylaxis, and this should be taken into account when evaluating the benefits (and risks) of antibioprophylaxis in children with high-grade VUR.

In conclusion, we recommend not performing a VCUG in infants ≤3 months of age with a first febrile UTI secondary to an *E. coli* pathogen associated with a normal renal US. In this group of infants, a VCUG can be safely postponed until the occurrence of a second febrile UTI. VCUG should be performed in infants with a non-*E. coli* UTI associated with an abnormal renal US. However, in the group of patients with an *E. coli* UTI associated with an abnormal renal US and in the group of patients with a non-*E. coli* UTI associated with a normal renal US, a prospective study should be performed to define the role of VCUG.

Contributors JYP, HC and MG: conceptualised and designed the study, participated in data analysis, drafted the initial manuscript and approved the final manuscript as submitted. CK and FC: participated in data analysis, participated in drafting the manuscript and approved the final manuscript as submitted. EG: participated in conceptualising, critically reviewed the manuscript and approved the final manuscript as submitted.

Competing interests None declared.

Patient consent This is a retrospective study and all data were retrieved through our coding system. Consent are obtained from parents.

Ethics approval The study was approved by the local ethic committee (number 74/14)

Provenance and peer review Not commissioned; externally peer reviewed.

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