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Original Articles

How Do the Revised Guidelines on Management of Urinary Tract Infection in Young Children Work in the Local Population?

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Abstract The purpose of follow up imaging study after first febrile urinary tract infection (UTI) is to detect urological abnormalities that need timely diagnosis and treatment. Recent guidelines attempt to recommend imaging in high risk children while avoiding unnecessary investigation in children who do not need them. This study retrospectively surveyed a local cohort of 820 children who had first febrile UTI when aged below 24 months and who had underwent full imaging studies. Significant urological abnormalities were found in 58 patients (7.1%), including 9 requiring surgical treatment, 37 with grade IV-V vesicoureteral reflux (VUR) and 12 with severe renal scarring. Four imaging strategies were tested in terms of number of imaging needed and the risk of missing the 58 target patients: The first strategy (ultrasonography (USG) for all patients and voiding cystourethrogram (VCUG) for those with abnormal USG or UTI recurrence) would need VCUG in 87 patients and missed 24% of the target patients (1.7% of whole cohort). The second strategy (USG for all patients and VCUG for those with clinical risk factors or USG

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abnormalities or UTI recurrence) would require 272 patients undergoing VCUG and missed 12% of the target patients (0.8% of cohort). The third strategy (USG and a late dimercaptosuccinic acid (DMSA) scan for all patients, and VCUG for those with USG or DMSA abnormalities or UTI recurrence) would require 133 patients undergoing VCUG and missed 12% of the target patients (0.8% of whole cohort). The last strategy (USG and late DMSA for all patients, and VCUG for those with clinical risk factors or USG or DMSA abnormalities or UTI recurrence) would require 298 patients undergoing VCUG and missed 8.6% of the target patients (0.6% of whole cohort). *Conclusion:* It is clearly not cost-effective to do full imaging (USG, VCUG and DMSA) in all young children after first febrile UTI. However, the extent of workup depends on the doctors' and the parents' value judgement balancing the cost of imaging studies versus the risk of missing abnormalities. This report shows that UTI is indeed a signal of underlying abnormalities in 7.1% of patients. It also provides an estimate of the risk of missing such abnormalities with various imaging strategies. This will be useful for counselling parents on follow up plans for such children.

Key words DMSA; Guidelines; Ultrasound; Urinary tract infection; Voiding cystourethrogram

Introduction

The management of urinary tract infection (UTI) in young children has changed dramatically in the past few years because of changes in the understanding of vesicoureteral reflux (VUR) and renal scarring, and because of the availability of data from randomised controlled trials of antibiotic prophylaxis in VUR[1-6] Thus several Guidelines on Management of Urinary Tract Infection have been published by national bodies from the UK[7], Italy,[8] Australia,[9] and the USA.[10] Despite this, the recommendations on follow up imaging studies, specifically whether voiding cystourethrogram (VCUG) is necessary for children with first UTI, still vary among these Guidelines. The question of whether to perform VCUG to detect VUR is a matter of value judgment, and physicians and parents have to arrive at a joint decision that balances the cost and discomfort and potential side effects of the VCUG versus the risks of missing underlying urological abnormalities that require early detection and timely medical or surgical interventions. To enable proper counselling of parents, the physician should know not only the risk of VCUG but also the prevalence of underlying abnormalities in these patients especially for the local childhood population.

This brief report aims to provide an estimate of the percentage of significant urological abnormalities in a local cohort of Chinese infants who had their first febrile UTI at the age of 24 months or below. We also estimate the chance that these abnormalities would have been missed if different imaging strategies were followed, paired with the number of investigations that need to be done with each strategy.

Patients and Methods

The study cohort included all children who were diagnosed to have febrile UTI for the first time at age 24 months or less. The patients were identified by searching hospital discharge databases of eleven paediatric units of public hospitals in Hong Kong from 1 January 2005 to 31 December 2006. Thus the cohort was a representative sample of the local childhood population. The previous guideline on UTI management in Hong Kong public hospitals[11,12] recommended that children presenting with fever without an obvious infective focus would undergo urinalysis screening. If urinalysis showed positive leucocyte esterase or nitrite on dipstix or positive white cells or bacteria on urine microscopy, these patients would have proper urine collection by suprapubic aspiration, catheterisation, or clean void technique. The urine sample was sent for culture and antibiotic sensitivity tests. Diagnosis of UTI was confirmed by the presence of fever, positive urinalysis (including dipstix for leucocyte esterase and nitrite and/or microscopy for leucocytes and bacteria) and significant urine culture of a properly collected urine sample. After successful treatment of UTI, all patients below 24 months of age with confirmed first febrile UTI would undergo ultrasonography (USG) and VCUG as soon as possible. Dimercaptosuccinic acid (DMSA) would be done after 4-6 months if VUR was identified on VCUG. Otherwise DMSA scan was optional. Patients with known urological abnormalities were excluded since they would have already undergone detailed imaging.

A total of 820 patients were included in the study. The presenting clinical features, laboratory and imaging results,

and follow up data including UTI recurrence and further medical/surgical treatment were recorded. The imaging studies were conducted and reported by radiologists in each study centre. USG assessment included renal length, pelvicalyceal or ureteric dilatation, pre- and post-void bladder volumes. The magnitude of renal pelvic dilatation was defined by the maximal antero-posterior diameter (APD) of the pelvis measured in the transverse plane, and APD of >5 mm was defined as abnormal. For VCUG, VUR, bladder trabeculation and urethra were assessed. VUR was graded according to the International Reflux Study Grading as grade I to V.[13] For DMSA abnormalities, each kidney was graded as follows: 1) one focal defect; 2) more than one focal defects; 3) small kidney without focal scars but differential glomerular filtration rate (GFR) was <45%; 4) small irregularly scarred kidney with differential GFR 10-40%; 5) non-functioning kidney with differential GFR <10%. Normal differential function should be 50±5%.

We have previously reported the demographics and results of investigations (USG, VCUG and DMSA) of this cohort of patients and evaluated the accuracy of the NICE Guideline in picking up urological abnormalities.[14] However, recent RCTs and the AAP meta-analysis have proven the absence of benefit of antibiotic prophylaxis in VUR of grade III or below.[10] For grade IV VUR, the number was still not statistically sufficient to exclude potential benefit. Hence in this report, we have narrowed our definition of significant urological abnormalities to include: 1) pyeloureteric junction, vesicoureteric junction or bladder neck obstructive uropathies; 2) other conditions that required surgical treatment; 3) VUR of grade IV or V, since they might benefit from antibiotic prophylaxis; 4) severe renal scars (with 2 or more focal scars or differential GFR of <40%), since long term follow up for these patients is warranted.

We reported the percentage of significant urological abnormalities as defined above. We also tested how effective the imaging strategy as recommended by the AAP Guideline was able to identify these abnormalities. In accordance with the AAP Guideline, an USG scan would be recommended for these patients, and only those with USG abnormalities or with UTI recurrence would be subjected to VCUG.

Secondly we tested whether the addition of clinical risk factors to the screening strategy would improve the effectiveness in picking up significant abnormalities. Clinical risk factors were defined as the presence of 1) clinical septic shock or proven septicaemia; 2) palpable abdominal mass; 3) impaired baseline renal function; 4) history of abnormal urine stream; 5) UTI due to non-*E.coli* organisms; 6) no clinical response to appropriate antibiotic treatment within 48 hours; and 7) history of VUR in first degree relatives (see Table 1). In the second strategy tested, patients will undergo VCUG if clinical risk factors are present, and then late DMSA if VUR is detected.

Thirdly we tested the strategy of doing USG and late DMSA (at 4-6 months after UTI) for all patients, regardless of their clinical risk factors, so as to select patients for VCUG.

Fourthly we also tested the strategy of using abnormal USG, plus clinical risk factors, plus abnormal late DMSA scan to select patients for VCUG. The different imaging strategies and outcomes are shown in Table 2.

Statistical Analysis

Nominal or categorical data were presented as percentages. For patients with bilateral renal abnormalities, they were categorised according to the VUR grade of the more severe side or worse APD values. We estimated the prevalence of significant urological abnormalities from the findings of USG, VCUG and DMSA. We then calculated in sequence the sensitivity, specificity, positive and negative predictive values, and reported the diagnosis of missed patients of the following selection strategies: 1) USG abnormalities alone, and 2) clinical risk factors OR USG abnormalities, and 3) USG OR late DMSA abnormalities; and 4) clinical risk factors OR USG OR late DMSA abnormalities in diagnosing urological abnormalities.

Table 1 Clinical risk factors at presentation identified in the 820 patients with first febrile urinary tract infection (UTI)

Risk factors	Number of patients (%) N=820
Shock/proven septicaemia (shock = 63; +ve blood culture = 20)	78 (9.5%)
Abdominal mass (kidney = 2; bladder = 0)	2 (0.2%)
Renal impairment (high serum creatinine)	37 (4.5%)
Poor urine stream	2 (0.2%)
Non-*E.coli* UTI	103 (12.6%)
No response to appropriate antibiotics in 48 hours	46 (5.6%)
Vesicoureteral reflux in first degree relatives	Not assessed
Any risk factor present	222 (27%)

Results

A total of 820 patients were recruited in the analysis. There were 576 boys and 244 girls, with a median age of 3.8 months. All underwent USG and VCUG. DMSA were performed in 75% and omitted in the remaining who had normal USG and VCUG (they were assumed to have normal DMSA). USG abnormalities were reported in 73 patients (8.9% of 820). VCUG showed VUR in 24% (grade I, II, III, IV, V VUR were reported in 5.7%, 7.6%, 6%, 3.9% and 0.6%, respectively). There were increasing incidences of abnormal DMSA with increasing grades of VUR. The percentages with abnormal DMSA in patients with no VUR, and VUR of grade I, II, III, IV and V were 5.4%, 8.3%, 17.3%, 20.8%, 65.5% and 80%, respectively.

There were 58 patients with significant urological abnormalities (7.1% of 820). Their diagnostic categories are shown in Table 3. These are the "target" patients whom

Table 2 Ability of three different imaging strategies to pick up urological abnormalities in young children after first febrile UTI (total N=820; number with urological abnormalities=58)

Strategy	USG for all patients → VCUG if USG abnormal OR UTI recurs	USG for all patients → VCUG if patient had risk factors OR USG abnormal OR UTI recurs	USG and late DMSA for all patients → VCUG if USG OR DMSA abnormal OR UTI recurs	USG and late DMSA for all patients → VCUG if patient had risk factors OR USG OR DMSA abnormal OR UTI recurs
Cases detected by initial criteria	28	43	49	51
Cases detected because UTI recurred	16	8	2	2
Missed cases	14	7	7	5
No. of patients who would have needed VCUG	87	272	133	298
No. of patients who would have undergone DMSA	44	51	820	820
Missed cases as percentage of whole cohort	1.7%	0.8%	0.8%	0.6%
Missed cases, as percentage of patients with significant abnormalities	24.1%	12.1%	12.1%	8.6%
Diagnosis of the missed cases	• 10 patients with grade IV VUR (bilateral in 6, unilateral in 4; 3 patients had renal scars) • 2 patients with grade II or III VUR but severe scarred left kidney (different GFR 36.5% and 23%, 1 required ureteric reimplantation) • 1 patient with xantho-granulomatous pyelonephritis requiring nephrectomy • 1 patient with bladder outlet obstruction requiring incision	• 5 patients with grade IV VUR (bilateral in 3, unilateral in 2; 1 had renal scar) • 1 patient with xantho-granulomatous pyelonephritis requiring nephrectomy • 1 patient with bladder outlet obstruction requiring incision	• 6 patients with grade IV VUR (bilateral in 4, unilateral in 2; all had no renal scar) • 1 patient with bladder outlet obstruction requiring incision	• 4 patients with grade IV VUR (bilateral in 2, unilateral in 2; all had no renal scar) • 1 patient with bladder outlet obstruction requiring incision

USG: ultrasonography; VCUG: voiding cystourethrogram; DMSA: dimercaptosuccinic acid; UTI: urinary tract infection; VUR: vesicoureteral reflux; GFR: glomerular filtration rate

we would wish to identify in any imaging strategy.

Table 2 shows a summary of the patients who need to undergo VCUG, and patients who would be detected by the four imaging strategies, and the cases that would have been missed in each strategy. If USG was performed after first febrile UTI, as recommended by the AAP Guideline, we would have detected 28 patients with significant urological abnormalities, with sensitivity 48%, specificity 94%, positive predictive value (PPV) 39%, negative predictive value (NPV) 96%. Of the 30 target patients with normal USG, 16 patients had UTI recurrence at a median of 4.6 months (range 0.1 to 28 months). Thus 14 patients would still remain undetected (1.7% of whole cohort of 820 patients; or 24.1% of 58 patients with urological abnormalities). As shown in Table 2, five patients had various degrees of renal scarring and two patients required surgical interventions.

Of the 820 patients, a total of 222 patients had clinical risk factors on presentation (Table 1). Of those with no risk factors, 42 had abnormal USG. If these risk factors plus USG were used as screening criteria, we would have to do VCUG in 264 patients, and would have detected 43 patients (sensitivity 74%, specificity 71%, PPV 16%, NPV 97%). On follow up, 8 of the remaining 15 patients developed recurrent UTI. Thus 7 patients would still have escaped our detection (0.84% of whole cohort; or 12.1% of the 58 patients with abnormalities), including 1 with renal scar and 2 requiring surgical intervention.

The third strategy tested was using both USG and late DMSA (done at 4-6 months after UTI) as screening criteria to identify significant urological abnormalities. Overall 49 target patients had either abnormal USG or DMSA (sensitivity 84%, specificity 89%, PPV 37%, NPV 99%). Of the 9 patients missed, 2 patients had recurrence of UTI. Thus 7 patients remained undetected (0.84% of 720; or 12.1% of the 58 patients with abnormalities). However in this scenario, we are confident that the missed cases had normal kidneys and had no recurrent UTI.

We also tested the fourth strategy of using clinical risk factors OR abnormal USG OR late DMSA as screening criteria to identify the target patients. We would have detected 51 of the target patients (sensitivity 88%, specificity 68%, PPV 17%, NPV 99%). Of the 7 patients missed, 2 had UTI recurrences and hence 5 patients remained undetected (0.6% of whole cohort or 8.6% of 58 patients with abnormalities). However, as shown in Table 2, the addition of clinical risk factors would have led to many more patients undergoing VCUG.

Discussion

With the rapidly changing concepts of childhood UTI and VUR, new guidelines on its management have been issued by various national bodies. The most important variations in these guidelines were on recommendations of follow up imaging after a first febrile UTI in young children. The NICE Guidelines recommended a rather complicated algorithm to order USG, DMSA and VCUG depending on the patient's age, presence of atypical features and recurrence of UTI.[7] Along a similar approach, the Australian and Italian guidelines also recommended USG and VCUG if the patient has risk factors suggesting a higher risk of VUR or UTI recurrence.[8,9] In contrast, the latest AAP Guideline

Table 3 Patients with significant urological abnormalities (that required additional medical or surgical intervention)

Significant urological abnormalities	No. of patients	Remarks
Obstructive uropathy	5	Pyeloureteric junction obstruction requiring pyeloplasty (2), vesicoureteral junction obstruction requiring reimplantation (3)
Bladder outflow obstruction	1	VCUG showed abnormal urethra (required endoscopic incision)
Other surgical procedures	3	Renal abscess with drainage done (1), nephrolithiasis requiring pyelotomy and extracorporal shock wave lithotripsy (1), xanthogranulomatous pyelonephritis requiring nephrectomy (1)
Grade IV-V vesicoureteral reflux	37	Grade IV VUR (32); Grade V VUR (5), with severe scarring (differential GFR <40%) in 14 patients, nephrectomy in 2 and ureteral reimplantation in 4 patients
Severe renal scarring (but no VUR or only Grade I-III VUR)	12	unilateral scar with differential GFR <40%, 5 had VUR Grade III, 2 had VUR Grade II, 1 had VUR Grade I, 4 had no VUR
Total	58	7.1% of 820 patients

VCUG: voiding cystourethrogram; VUR: vesicoureteral reflux; GFR: glomerular filtration rate

recommended USG alone for all patients and VCUG was reserved for patients with abnormal USG findings or UTI recurrence.[10] However, these recommendations were mainly opinion-based, balancing the perceived risks of VCUG versus the risk of missing urological abnormalities. This study attempts to test how well these recommendations would be able to identify significant urological abnormalities in a local cohort of young Chinese children who had first febrile UTI when aged 2 years or below.

We have included not only lesions that required surgical treatment but also grade IV-V VUR and severe renal scarring as significant urological abnormalities. Admittedly the inclusion of the last two categories is controversial. The meta-analysis of 1091 young children with VUR, obtained from six previously published randomised controlled trials by the AAP showed that there was no benefit of antibiotic prophylaxis on the rate of recurrent UTI in all grades of VUR. However, grade V VUR was not studied in the meta-analysis because of too few patients, and the group with grade IV VUR consisted of only 55 patients in the antimicrobial group and 49 patients in the control group, which we considered as inadequate sample size. To achieve an alpha of 0.05 and power of 80%, assuming a risk difference of 15% to be clinically significant reduction in UTI recurrence, a total sample size of 226 should be recruited in a randomised controlled trial. Moreover, apart from antibiotic prophylaxis, there may also be other modalities of treatment, such as surgical correction of VUR, which may be effective in prevention of UTI recurrence and renal damage. Although the long term significance of isotope uptake defects on DMSA scans is still uncertain, they are generally recognised as indicative of renal damage and this would have placed these patients into the category of chronic kidney disease stage I, so that they would benefit from long term monitoring for signs of progressive renal deterioration and hypertension.

Our study showed that in young children with first febrile UTI, the risk of having significant urological abnormalities (as defined above) was 7.1%. According to the AAP Guideline, the patient would undergo an USG and then be followed up. Twenty-eight of the 58 patients (48%) would be picked up because of USG abnormalities, and 16 more patients would develop UTI recurrences. Thus, if applied to our cohort, the AAP Guideline would miss urological abnormalities in 1.7% of the 820 patients or 24.1% of all patients with significant urological abnormalities in this cohort. These patients might potentially benefit from early detection and timely treatment. Thus we have reservation in recommending this strategy.

Similar calculations using clinical risk factors plus USG abnormalities as screening criteria for performing VCUG, as advocated by the NICE, Italian or Australian guidelines, indicated that we would be able to detect 43 patients by the screening criteria, and 8 more patients would need VCUG because of UTI recurrence, thus we would miss urological abnormalities in only 0.8% of the cohort. The cost would be doing VCUG in 272 patients.

We also tested a third approach of using either USG or DMSA abnormalities as screening criteria for VCUG, as had been recommended by the Swedish group though they suggested doing DMSA early.[15,16] One hundred thirty-one patients would undergo VCUG because of USG or DMSA abnormalities and we would detect 49 patients with urological abnormalities. Of the 9 patients missed, 2 had UTI recurrences. With this approach, we would have detected all target patients except 7 (0.8%). Moreover the missed cases were patients with grade IV VUR and they were probably not clinically problematic cases since they had no renal scars and no UTI recurrence. This strategy is recommendable since it can reduce the number of patients being subjected to the invasive VCUG, and yet can keep a comparable false negative rate.

The fourth strategy of doing VCUG for patients with either clinical risk factors, or USG abnormalities, or DMSA abnormalities, or for those with UTI recurrences, would miss only five patients with urological abnormalities (0.6%). However, the cost would be the need to do DMSA for all 820 patients and VCUG in 296 patients. As shown in Table 2, the criteria of clinical risk factors had low specificity, and its inclusion would have subjected more than double the number of patients undergoing VCUG compared to other strategies with clinical risk factors.

We could also explore the option of doing USG and DMSA for all patients, but limited VCUG only to patients with "clinical risk factors" AND "either abnormal USG OR DMSA scans". With this approach, 57 patients would undergo VCUG with detection of 31 of the 58 target patients. In addition, 4 patients were already identified on DMSA. Of the remaining 23 patients, 14 had recurrent UTI and underwent VCUG. Although the need for VCUG was largely reduced to 70, this approach missed 9 patients with significant urological abnormalities (1% of cohort). These included 8 patients with grade IV or V VUR (5 bilateral, 3 unilateral, but no renal scarring) and one patient with urethral obstruction requiring incision. In our cohort, this theoretical approach led to missing 3 patients with surgical conditions until they had recurrent UTI. Comparing with strategy 3, using risk factors as an added screening factor together with

either abnormal USG or abnormal DMSA, or UTI recurrence, we would have reduced the number of VCUG needed to nearly half (from 133 to 70), while the missed cases as a percentage of the whole cohort would have only increased slightly from 0.8% to 1.0%. Such an approach might be considered when parents have concerns of doing VCUG. On the other hand, patients with dilated renal pelves on USG would need to be investigated for obstructive uropathies if indicated even if VCUG was not done.

Some limitations of our study included its retrospective nature. Thus clinical risk factors in some patients might have been missed because of incomplete documentation. Some patients might have UTI recurrences that were treated by other doctors and hence not known to the parent unit. The USG, DMSA and VCUG were not reported by the same radiologist and there might be variations especially for USG which was operator dependent. The exclusion of grade III VUR as a significant urological abnormality was based on the AAP meta-analysis which showed an overall lack of benefit of antibiotic prophylaxis. However, in the RCT reported by Craig et al,[5] an absolute risk reduction of 6% was reported, and in the Swedish Reflux Study,[6] prophylaxis was beneficial, in terms of reduction in UTI recurrence and DMSA deterioration, in girls with grade III-IV VUR. This approach might have left out some patients who would have benefited by the screening.

In conclusion, it is generally accepted that children with UTI but normal urinary tract, if adequately treated, seldom suffers renal damage. It is clear that not all children with first febrile UTI need full imaging studies, especially VCUG, and antibiotic prophylaxis. Whether children considered as being at high risk of VUR or UTI recurrences should undergo VCUG is a matter of value judgement. For the guideline developer, one has to consider the cost of recommending VCUG for too many patients in order not to miss the few with significant abnormalities. On an individual basis, parents have to balance the discomfort and potential complications of VCUG versus the risk of leaving a significant urological abnormality undetected and untreated in their children. For those patients with USG abnormalities or recurrent UTI, most guidelines recommend VCUG. Whether the presence of clinical risk factors at presentation warrants a VCUG is controversial and decision should be based on physician and parental preference. Lastly for the individual patient, DMSA may be a reasonable second screening in patients with clinical risk factors, before proceeding to the invasive VCUG, though cost-effectiveness consideration would be against the recommendation of doing DMSA for all patients.

Declaration of Interest

We declare that we have no conflict of interests.

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