

Boys Under 6 Months Presenting with their First Febrile Urinary Tract Infection

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Background and Introduction

Urinary tract infections are common in children and can cause morbidity. International and local guidelines differ in their recommendations for the investigation of infants following a first febrile UTI, especially for those under 6 months of age. In particular, most medical guidelines do not offer any recommendation for early surgical referral. We looked at a cohort of boys less than 6 months of age presenting with their first UTI and sought to determine whether any features in the investigation paradigm should alert a paediatrician to consider early referral to paediatric surgery.

Method

We performed a retrospective analysis of all boys less than 6 months of age presenting with their first febrile UTI to the emergency department of Mater Dei Hospital in the period between January 2020 to December 2021.

Results

38 boys were included. All underwent a renal US: 13 (34%) had an abnormal US. An MCUG was abnormal in 72.7% of boys with an abnormal US vs 32% of those with a normal US, but this was not statistically significant. DMSA was more likely to be abnormal in those with an abnormal US and abnormal MCUG; all boys with a normal US and normal MCUG had a normal DMSA scan. Twelve boys underwent cystoscopy: 11 had abnormal findings. Only 1 boy had previous normal US and MCUG; all the rest had an abnormal MCUG with/without an abnormal US. 9 boys with positive findings on cystoscopy were aged 2 months or less with a median age of 7 weeks at presentation.

Conclusion

For this cohort we determined that one should proceed to an MCUG even if the US findings are normal; a DMSA scan is not helpful in deciding whether to proceed to cystoscopy; the 'top-down' approach for investigation should not be advocated for boys less than 2 months of age; boys with first febrile UTI aged 2 months or less should be referred for consideration of cystoscopy.

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Urinary tract infection (UTI) in children is a common and potentially serious condition that may be difficult to recognise, particularly in infants in whom obtaining and interpreting samples may be challenging. Signs of UTI in infants are non-specific and include fever, vomiting, lethargy, irritability, poor feeding, failure to thrive, haematuria and foul-smelling urine. Urine dipstick demonstrates raised leucocytes and positive nitrites (although the latter may be falsely negative since neonates and infants void frequently), urine microscopy of uncontaminated urine shows pyuria and bacteriuria, and urine culture shows a growth of a single organism with >10(5) colony forming units/ml.

UTI in the neonatal period has a male predominance and infections are more frequently caused by non-*Escherichia coli* organisms with a higher risk of urosepsis.¹ Incidence of UTI in boys is highest during the first 6 months (5.3%), while the converse occurs in girls with an incidence of 2% in the first 6 months.¹ *Escherichia coli* remains the commonest causative organism, however atypical organisms have been associated with congenital renal tract abnormalities. A UTI can be the first presentation of a congenital structural abnormality of the urinary tract,² which risks long term consequences including renal scarring. In fact, each febrile UTI increases the risk of renal scarring by 2.8%.¹ The investigations and follow up of UTI in children have been widely debated. Such investigations need to be evidence based, minimally invasive and judicious as they place a heavy burden on health care resources. Investigations can also be an unpleasant experience for both parents and infants. Internationally and locally, published guidelines endeavour to minimise unnecessary investigations in infants and are based on age group and gender, on whether an infection is typical or atypical and on whether an infection is recurrent. Most guidelines do not include any recommendations for surgical referral, and we set out to investigate which cohort of boys with first presentation of urinary tract infection benefits from a surgical review.

38 male cases	
Age cohort	Number of cases
< 2 months	12
2-3 months	13
3-6 months	13

Table 1 Age cohorts of male cases presenting with first UTI <6 months of age

MATERIALS AND METHOD

We performed a retrospective analysis of all admissions to Mater Dei Hospital with a first UTI in the period from January 2020 to December 2021. Data was obtained from handover documents of ward admissions, from iSOFT clinical manager, discharge letters and notes and included age of presentation, gender, urinalysis results, micro-organism grown from urine culture and imaging results including renal ultrasound (US), micturating cystogram (MCUG) and dimercaptosuccinic acid scan (DMSA). Findings at cystoscopy were documented. Use of antibiotic prophylaxis was studied. Patients already under investigation for congenital anomalies of the kidney and urinary tract were excluded.

RESULTS

There were 62 admissions with first time UTIs in infants less than 6 months old between January 2020 and December 2021. 38 cases were male (61.3%) as shown in **Table 1**. Of these, 12 (31.6%) were <2 months old, 13 (34.2%) were 2-3 months old and 13 (34.2%) were 3-6 months old at the time of admission.

Urinalysis

24 boys (63.2%) had a positive urinalysis result (elevated leucocytes, nitrite positive), whilst 5 boys (13.1%) had an equivocal urinalysis result (mildly elevated leucocytes, nitrite negative). 9 cases (23.7%) had a negative urinalysis result but had a growth on urine culture. 36 out of the 38 boys had a positive culture. In 2 boys (5.2%) the urine sample was contaminated but the urinalysis was strongly suggestive of a UTI.

Cultures

Escherichia coli was the commonest growth (61.5%) followed by *Klebsiella pneumoniae* (15.4%), ESBL positive *Escherichia coli* (7.7%), *Klebsiella oxytoca* (2.6%), *Streptococcus agalactiae* (2.6%), *Morganella morganii* (2.6%) and *Proteus mirabilis* (2.6%), as shown in **Figure 1**.

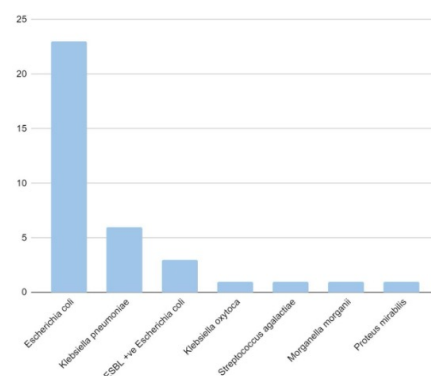


Figure 1 Bacterial culture growths of males presenting with first UTI <6 months

Four boys presented with urosepsis with *Escherichia coli* (50%) and *Klebsiella pneumoniae* (50%) cultured from both blood and urine.

Ultrasound Scan

All 38 boys underwent a renal ultrasound. 13 cases (34.2%) had an abnormal ultrasound: kidney size discrepancy in 3 (7.9%), hydronephrosis +/- distal dilated ureter/s in 6 (15.8%), pelvi-calyceal splitting in 2 (5.3%), evidence of pyelonephritis in 1 (2.6%) and incidental urachal remnant in direct connection with bladder in 1 (2.6%). 25 cases (65.8%) had normal ultrasound findings.

MCUG

An MCUG was performed in 36 cases (94.7%). Of the 13 boys with an abnormal ultrasound, 11 had an MCUG and this was abnormal in 8 cases (72.7%; 95% CI: 39-92%) (Table 2). Two boys did not undergo an MCUG (one had kidney size discrepancy and the other had a urachal remnant). All 25 boys with a normal US underwent an MCUG and this was abnormal in 8 (32%; 95% CI: 16-35%). This did not reach statistical significance, $p = 0.034$ (Fisher's exact test).

DMSA scan

A DMSA scan was performed in 26 cases (68.4%), with the findings shown in Table 3. In 7 cases (18.4%), the procedure was either refused, or the patient did not turn up.

Considering the 8 boys with an abnormal US and abnormal MCUG, DMSA was performed in 7 and was abnormal in 4. Considering the 8 boys with a normal US and abnormal MCUG, DMSA was performed in 7 and was abnormal only in 1.

Diethylenetriamine/Mercaptoacetyl triglycine (DTPA/MAG3 scan)

A DTPA or MAG3 scan was not performed in any of the cases identified.

Cystoscopy

12 of the 38 boys (31.6%) eventually proceeded to a cystoscopy - 11 had abnormal findings (Table 4). Six of the 8 boys with an abnormal US and abnormal MCUG underwent cystoscopy which was abnormal in 5 (83%). Five of the eight boys with a normal US and abnormal MCUG underwent cystoscopy which was abnormal in all (100%).

One boy with normal US, normal MCUG and normal DMSA scan underwent cystoscopy because of a complex presentation (presented with recurrence of symptoms while still recovering from the first

Table 2 MCUG findings

MCUG in cases with abnormal US findings	MCUG in cases with normal US findings
4 Dilated posterior urethra	1 Dilated posterior urethra
1 Bilateral VUR (grade 4)	3 Bilateral VUR (grade 3 in 1, grade 4 in 2)
2 Unilateral VUR (grade 4 in 1, grade 5 in 1)	4 Unilateral VUR (grade 1 in 1, grade 2 in 1, grade 3 in 2)
1 Urinary diverticulum	17 normal
3 Normal	
2 Not performed	

Table 3 DMSA findings

DMSA findings			
Abnormal US + Abnormal MCUG n = 7	Abnormal US + Normal MCUG n = 2	Normal US + Abnormal MCUG n = 7	Normal US + Normal MCUG n = 10
2 Smaller left kidney with reduced function (38%)	1 Smaller right kidney with normal function	1 Horseshoe kidney with no cortical scarring	10 Normal
1 Duplex left kidney with smaller lower moiety and global reduction in uptake (34%)	1 Normal	6 Normal	
1 Smaller left kidney with normal function			
3 Normal			

Table 4 Cystoscopy findings according to age at presentation

Cystoscopy findings	
≤ 2 months of age	> 2 months of age
5 PUV	1 PUV
3 Bilateral VUR	1 Bilateral VUR
1 Unilateral wide ureteric orifice	1 Normal

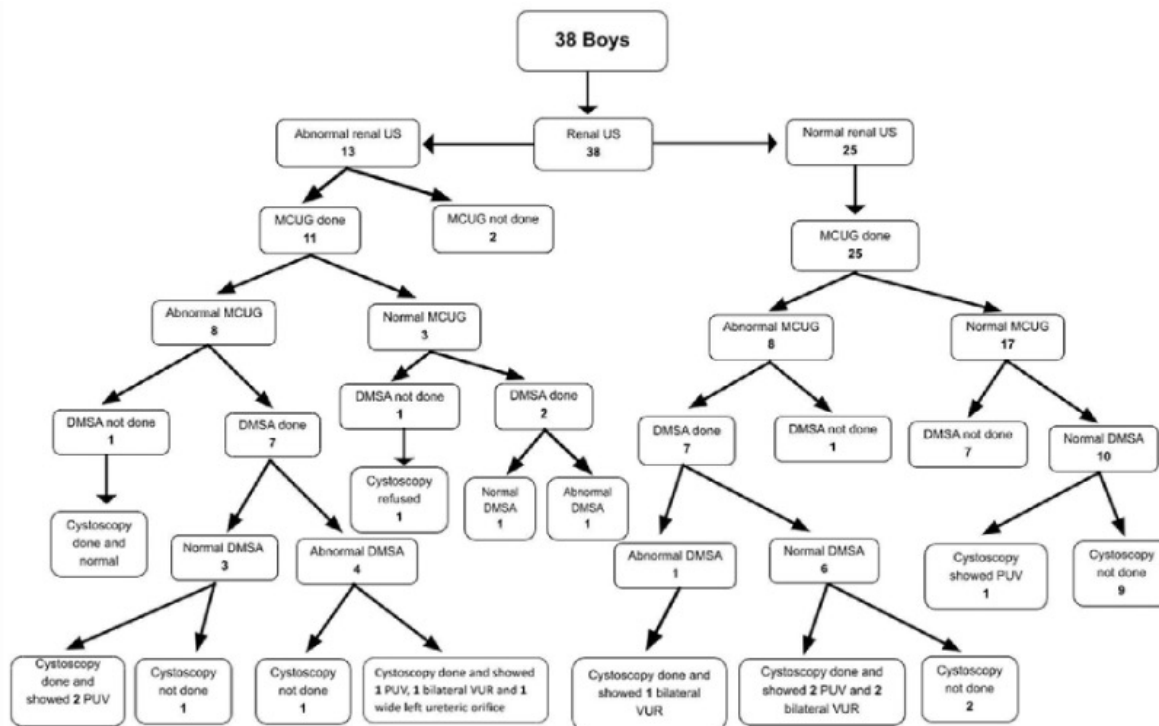


Figure 2 Flow chart demonstrating imaging performed and findings

presentation) and posterior urethral valves were diagnosed at cystoscopy. 9 boys with positive findings on cystoscopy were aged 2 months or less with a median age of 7 weeks at presentation.

Figure 2 demonstrates the imaging performed and their findings.

Prophylaxis

25 boys (65.8%) presenting with first UTI at <6 months of age were started on prophylaxis at presentation: trimethoprim/sulfamethoxazole (55.3%), nitrofurantoin (7.9%) or ciprofloxacin (2.6%). Diagnoses included: posterior urethral valves⁶, high grade vesico-ureteric reflux⁶, low grade vesico-ureteric reflux², bladder diverticulum¹, dilatation of the posterior urethra on MCUG¹, pelvicalyceal splitting on US¹, renal size discrepancy on US and DMSA¹, mild hydronephrosis and bilateral ureteric dilatation on US¹ and 6 cases with normal investigations.

5 cases with confirmed PUV had a urinalysis which was clearly suggestive of a UTI (1 only had mildly elevated leucocytes and nitrites negative) but all cases had *Escherichia coli* on urine culture.

For the 9 cases with a negative urinalysis but a positive urine culture, 2 cases had low grade vesico-ureteric reflux on MCUG, 1 case had an incidental urachal remnant on renal US scan and 1 case had mild

pelvicalyceal splitting of one kidney on renal US. The rest had normal findings on imaging.

DISCUSSION

Urinary tract infection is one of the commonest bacterial infections in childhood with congenital anomalies of the kidney and urinary tract being a major risk factor. International and local guidelines have been published to describe the presentation, diagnosis and management of such infections. An attempt is made to determine which children will benefit from further investigation and avoid painful procedures, parental worries and costly investigations when these are not necessary. The guidelines include recommendations for imaging depending on the clinical presentation, age and gender and the micro-organism grown. Infection is defined as typical or atypical, and recurrent. Most guidelines define an infection as being atypical if there is no response to treatment within 48 hours, if the child is septic/very unwell, if there are abdominal masses, if there is renal impairment, if there are signs of upper tract involvement or infection with a non-*Escherichia coli* micro-organism.

The guidelines differ in their recommendations for medical imaging: we therefore referred to 5 medical guidelines³⁻⁷ and 1 surgical guideline.¹ Of note, both the American and Italian guidelines exclude infants

<2 months of age citing that this cohort requires special considerations. Only one medical guideline gave recommendations on referral to paediatric urology. The South Australian Paediatric Clinical Practice Guidelines on UTI in Children recommends that referral should be considered urgently if there is suspicion of renal tract obstruction, high grade vesico-ureteric reflux, recurrent and atypical UTI, structural neurological abnormality or suspected neurogenic bladder.⁷ The Swedish guideline gives detailed recommendations for the management of VUR.⁸⁻⁹ The National Institute for Health and Care Excellence (NICE) does not recommend routine surgical management of VUR.³ We therefore studied a cohort of boys less than 6 months of age presenting with their first UTI to establish recommendations for referral for cystoscopy.

A cohort of 38 boys less than 6 months of age presenting to Mater Dei Hospital with their first febrile urinary tract infection was reviewed. We analysed the urinalysis and culture results as well as any ultrasound, MCUG and DMSA scan results. We documented cystoscopy findings of the boys who underwent the procedure.

For infants with a first UTI presenting before 6 months of age all the guidelines recommend a renal ultrasound (US). All boys in this cohort had a renal ultrasound and this was abnormal in 13 of 38 (34.2%). 72.7% of boys with an abnormal US had an abnormal MCUG; 32% of boys with a normal US had an abnormal MCUG. The yield of having an abnormal MCUG was thus higher when the US was also abnormal, however, this did not reach statistical significance ($p < 0.34$, Fisher's exact test). The fact that the numbers were small needs to be taken into consideration. The guidelines differ in their recommendation for performing an MCUG and the practice patterns have shifted considerably towards a less invasive approach in recent years¹⁰; the consensus in the medical guidelines is to perform an MCUG under the age of 6 months if the US is abnormal, if the presentation is atypical or if it is recurrent. The European Association of Urology and European Society for Paediatric Radiology guidelines go further and recommend an MCUG even with a normal renal US in infants <1 year to exclude VUR.¹¹ Our findings at MCUG in boys with an abnormal US included dilated posterior urethra and high grades of reflux of 4 – 5; with a normal US, MCUG findings included dilated posterior urethra and lower grades of reflux of 1 – 4, but which still constitute major findings. Hence, we conclude that an MCUG is indicated even if the ultrasound findings are normal.

Six of the 8 boys with an abnormal US and abnormal MCUG proceeded to cystoscopy and only one had a normal cystoscopy. The others all had major findings. Only 3 of these boys had an abnormal DMSA scan. Thus, findings at DMSA scan were not a good marker to identify boys with serious underlying abnormalities found on cystoscopy. Similarly, 4 of the 6 boys who had a normal DMSA scan with a normal US and abnormal MCUG and who proceeded to cystoscopy had posterior urethral valves or high grade bilateral VUR at cystoscopy. Hence, DMSA scan was not found to be helpful in deciding whether to proceed to cystoscopy or not. This is not to say that a DMSA scan is not useful in the management paradigm because the results do influence certain surgical decisions, for example, in the management of VUR, but this study has shown that an abnormal MCUG is more useful in deciding whether to proceed to cystoscopy or not. Two approaches in the imaging following a UTI have been put forward.¹² The 'top-down' approach (US followed by DMSA scan) looks for any scars which can correlate with high grade VUR and an MCUG is performed only if renal involvement is present. The 'bottom-up' approach (US followed by an MCUG) looks for bladder involvement to detect VUR. In our experience, the findings on DMSA scan did not correlate with the findings on cystoscopy and we would advocate the 'bottom-up' approach using US and MCUG in boys <6 months presenting with their first UTI in whom posterior urethral valves, besides VUR, need to be excluded.

One child with a normal renal US and MCUG and DMSA scan underwent cystoscopy and was found to have posterior urethral valves. He had presented with recurrent symptoms of UTI while still recovering from his first presentation, making it difficult to define whether this was an unresolved first febrile infection or a recurrent infection. Nonetheless, this was a complex presentation in a boy less than 3 months of age and highlights the recommendations by most guidelines to use clinical judgement and decide on a case-by-case basis when making decisions at this young age.

11 out of 12 cystoscopies performed were abnormal. Of note, 6 boys (50%) started out with a normal renal US. Of these, 5 had an abnormal MCUG and 4 had an abnormal DMSA scan. Six boys (50%) started out with an abnormal US. All had an abnormal MCUG and 3 had an abnormal DMSA scan. 9 boys with positive findings on cystoscopy were aged 2 months or less with a median age of 7 weeks at presentation. Thus, the top-down approach in boys less than 2 months of age is likely to miss those with significant findings on cystoscopy.

SUMMARY BOX

What is known:

- Perform a urine culture only when urinalysis is suggestive
- Renal US should be performed in all boys <6 months of age

What are the new findings:

- Perform an MCUG in all boys <6 months presenting with their first UTI even if the US is normal
- The sensitivity of DMSA scan after a first UTI is poor. Do not rely on a DMSA scan to decide whether to proceed to cystoscopy, therefore the top-down approach is not reliable in this age-group
- Boys <2 months of age should be recommended for cystoscopy
- New local guidelines must include detailed recommendations for antibiotic prophylaxis

Escherichia coli is a common pathogen in urinary tract infections since the bacteria have evolved a mechanism using fimbriae which allow them to attach to the urothelium and withstand the stresses of urine flow.¹³ Reports in the literature suggest that the presence of atypical micro-organisms such as *Klebsiella* and *Proteus* are more likely to be associated with underlying structural anomalies^{14,2} Nonetheless, in this study, 5 of the 6 boys who had posterior urethral valves at cystoscopy presented with a urinalysis which was suggestive of a UTI and *Escherichia coli* was grown in all. This cohort had a higher percentage of *Escherichia coli* cultured in cases of PUV when compared to other studies with rates of 26.7%.¹⁵ Hence, the presence of *Escherichia coli* does not preclude a serious underlying anomaly.

The boys with a normal urinalysis and a growth on culture all had minor findings on imaging. The guideline recommends that a urinalysis is first performed, and a culture is sent only if the urinalysis suggests a UTI. This has been shown to be a valid recommendation from this study.

CONCLUSION

This study has highlighted the importance of recommending boys less than 2 months of age for cystoscopy. It has also confirmed that a normal US does not exclude serious underlying abnormalities. The 'top-down' approach is not recommended in boys less than 6 months of age: a clear understanding of any bladder pathology is essential and an MCUG is best recommended. Local guidelines need to be updated with recommendations for cystoscopy and MCUG in our younger cohorts and with advice on antibiotic prophylaxis. Ultimately, we aim to establish consistent clinical practice by following evidence-based guidelines in order to reduce the number of unnecessary investigations which place a burden on the health services. We also aim to limit radiation exposure in neonates and infants, avoid unnecessary anxiety and stress to both the infant and the parents both when procedures are performed and while results are awaited.

Abbreviations

UTI	Urinary tract infection
PUV	Posterior urethral valves
VUR	Vesico-ureteral reflux
MCUG	Micturating cystogram
US	Ultrasound scan
DMSA	dimercaptosuccinic acid scan
DTPA/MAG3	Diethylenetriamine/ Mercaptoacetyltriglycine
NICE	National Institute of Health and Care Excellence

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