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Guideline Review

Introducing the Guideline on Management of Urinary Tract Infection in Children by the National Institute for Health and Clinical Excellence (NICE Guideline)

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Abstract

The concept and management of urinary tract infection in children has been evolving over the past decades. While previous guidelines advocated universal imaging and antibiotic prophylaxis for young children with first time urinary tract infection (UTI), the recent guideline issued by the National Institute for Health and Clinical Excellence in the United Kingdom in August 2007 recommended a more selective strategy. This article presents a summary of the NICE Guideline with comments and recommendations by the authors. The Guideline was stringently developed and has incorporated recent scientific findings. Compared to previous guidelines, the major changes include the following: Firstly, it presents a complex algorithm for the diagnosis of UTI by rapid bedside tests. Diagnosis does not require urine culture in children above 3 years old who show positive dipstix results. Secondly it adopts a selective imaging strategy after first UTI. Ultrasound was recommended for infants below 6 months, or children of any age with atypical or recurrent UTI. Dimercapto-succinic acid scan was recommended for infants below 3 years with atypical or recurrent UTI, and those above 3 years with recurrent UTI. Micturiting cystourethrogram was recommended only for infants below 6 months with atypical or recurrent UTI or with abnormal ultrasound, and for infants above 6 months with atypical or recurrent UTI AND a family history of vesicoureteral reflux (VUR), poor urine stream, non-E.coli infection, or dilated renal pelves. Thirdly, antibiotic prophylaxis or surgery was not recommended routinely for VUR treatment. The authors discuss several concerns and suggest the following modifications for local practice: that a pre-treatment urine culture is useful in treatment by identifying the pathogen and its antibiotic sensitivity; that an ultrasound scan is reasonable, if a patient has not had a reliable antenatal or postnatal ultrasound, to exclude obstructive uropathies. For imaging strategy after a first UTI, the NICE Guideline is a reasonable approach if parents accept the small possibility of missing severe VUR for which the optimal treatment is still undecided. Until further evidence is available, a prudent option is to continue full imaging for infants below 12 months old and recommend antibiotics prophylaxis for Grade IV-V VUR. Further research is

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needed to better define the best treatment for severe VUR and to devise an investigation strategy that can identify those patients who may benefit from early detection of VUR and its treatment, and at the same time avoid over-investigating and over-treating the remaining patients.

Key words Antibiotic prophylaxis; Child; Guideline; Urinary tract infection; Vesicoureteral reflux

Introduction

Urinary tract infection (UTI) is one of the commonest infections in young children and its management is probably one of the most controversial. The traditional concepts emphasised the beliefs that UTI often signals underlying urological abnormalities principally vesicoureteral reflux (VUR). Upper UTI (pyelonephritis) in association with gross VUR especially intrarenal reflux would lead to renal scarring as shown by animal experiments. Renal scarring was associated with long term sequalae such as hypertension, renal impairment and complications of pregnancy.

Thus previous guidelines were published by professional bodies such as the Royal College of Physicians of London,[1] the American Academy of Pediatrics,[2] and locally by a working group commissioned by the Paediatric Coordinating Committee in Hospital Authority.[3,4] These guidelines helped to standardise management and they advocated universal imaging of all young children after first time UTI, by ultrasound (USG), micturiting cystourethrogram (MCUG), and dimercapto-succinic acid scan (DMSA) depending on age and clinical features. Also long term antibiotics prophylaxis was advocated for VUR based on RCTs showing no difference between surgical reimplantation versus medical prophylaxis.[5-7]

These guidelines have been increasingly questioned as our understanding of UTI in children changed. It is now accepted that "renal scarring" as seen on DMSA or IVU could be either congenital (renal dysplasia, usually associated with gross VUR in a male baby) or acquired (usually recurrent pyelonephritis in a girl with dysfunctional voiding).[8-10] Universal USG after UTI seldom revealed findings that changed clinical management.[11] Moreover, universal MCUG to detect VUR were questioned because recent studies have shown that VUR was a weak predictor of renal parenchymal defects,[12] and that antibiotics prophylaxis for VUR conferred no benefit in the rates of recurrent UTI or renal scarring.[13] Despite universal imaging after UTI, the incidence of endstage renal failure from reflux nephropathy have not decreased in several national and international registries.[14]

With this changing background, the new NICE Guideline was published in August 2007 to reflect these changes.[15] This report summarises the key recommendations of the NICE Guideline. Where appropriate, the authors attempt to discuss areas where firm evidences are lacking and to provide an alternative management strategy for parents' consideration.

Summary Recommendations of the NICE Guideline

The NICE Guideline covers the scenario of first-time UTI in children of all ages but excluded those with known urological abnormalities. It was developed through a stringent process of guidelines development convened by the National Collaborating Centre for Women's and Children's Health in the United Kingdom. The Guidelines Development Group (GDG) consisted of experts from multiprofessional groups and also the lay public. By considering the clinical pathway of a child with possible UTI, the GDG identified a series of clinical questions for their further research. The full report described the formal process and findings of their literature search and systematic review of each clinical question, and the interpretation of the GDG. Based on these interpretations, the GDG made a series of key recommendations. Consultations were then sought from various stakeholder professional organisations and the recommendations were revised accordingly. The next section attempts to outline the key recommendations. For details, the readers are encouraged to refer to the full guideline especially the summary chapter.

Clinical Recognition and Diagnosis:

Who Should be Tested for UTI?

1a. Infants and children presenting with unexplained fever of 38°C or higher should have a urine sample tested after 24 hours at the latest.

1b. Infants and children with an alternative site of infection should not have a urine sample tested. When such a patient remains unwell, urine testing should be considered after 24 hours at the latest.

1c. Infants and children with specific symptoms and signs of UTI should have a urine sample tested (see Table 1 for presenting symptoms and signs).

What Urine Samples to Collect?

2a. A clean catch urine sample is recommended. Alternatives are urine collection pads, invasive methods e.g. catheter or suprapubic aspiration (SPA) samples. Ultrasound (USG) guidance should be used for SPA.

2b. In a seriously ill child, it is preferable to collect a proper urine sample for testing, but antibiotics treatment should not be delayed if it is unobtainable.

3. Urine should be cultured within 4 hours. Otherwise urine should be refrigerated or preserved with boric acid. The manufacturer's instructions should be followed when boric acid is used to ensure the correct sample volume to avoid potential toxicity against bacteria in the sample.

How to Make the Diagnosis of UTI in Children of Different Ages?

4. Diagnosis of UTI depends on symptoms plus positive urine culture but specific criteria of colony counts (CFU) was not mentioned.

4a. Infants below 3 months old should be under paediatric care. Investigations should include urgent urine microscopy and culture plus other sepsis workup (as specified in NICE guidelines for Feverish Illness[16]). Treatment is started for infants <1 month old, OR for infants aged 1-3 months AND clinically unwell and/or total WBC $<5x10^9$/L or $>15x10^9$/L, OR if UTI is diagnosed (see Table 2).

4bi. For children aged between 3 months to 3 years with specific symptoms and signs of UTI: urgent urine microscopy and culture should be sent, and treatment should be started (see Table 3).

4bii. For children aged between 3 months to 3 years with nonspecific symptoms and signs, management depends on clinical assessment of risk of serious illness according to NICE Guidelines for Feverish Illness:[16]

- high risk of serious illness (see Table 4) → workup and treatment as in 4a.
- intermediate risk of serious illness (see Table 4) → urine should be sent for urgent microscopy (or nitrite if urgent microscopy is not available) AND culture. Treatment should be started if urgent microscopy OR nitrite (on fresh urine) is positive.
- low risk of serious illness→urine urgent microscopy AND culture, and only treat if either is positive.

4ci. For children aged over 3 years (see Table 5), urine leucocyte esterase (LE) and nitrite tests are as diagnostic as microscopy/culture; hence

- UTI is diagnosed and antibiotics can be started if both LE/nitrite are positive. One should send urine culture ONLY if the child is seriously ill OR unresponsive to initial treatment OR has a history of recurrent UTI.

Table 1 Presenting symptoms and signs of UTI in children. (Reproduced from the NICE Guideline,[15] with the permission of the Royal College of Obstetricians and Gynaecologists.)

Age group		Symptoms and signs Most common ---------- Least common		
Infants younger than 3 months		Fever Vomiting Lethargy Irritability	Poor feeding Failure to thrive	Abdominal pain Jaundice Haematuria Offensive urine
Infants and children, 3 months or older	Preverbal	Fever	Abdominal pain Loin tenderness Vomiting Poor feeding	Lethargy Irritability Haematuria Offensive urine Failure to thrive
	Verbal	Frequency Dysuria	Dysfunctional voiding Changes to continence Abdominal pain Loin tenderness	Fever Malaise Vomiting Haematuria Offensive urine Cloudy urine

Table 2 Urine testing strategy for infants younger than 3 months. (Reproduced from the NICE Guideline,[15] with the permission of the Royal College of Obstetricians and Gynaecologists.)

All infants younger than 3 months with suspected UTI should be referred to paediatric specialist care and a urine sample should be sent for urgent microscopy and culture. These infants should be managed in accordance with the recommendations for this age group in 'Feverish illness in children' (NICE clinical guideline 47)

Table 3 Urine-testing strategy for infants and children 3 months or older but younger than 3 years. (Reproduced from the NICE Guideline,[15] with the permission of the Royal College of Obstetricians and Gynaecologists.)

Urgent microscopy and culture is the preferred method for diagnosing UTI in this age group; this should be used where possible	
If the infant or child has specific urinary symptoms	Urgent microscopy and culture should be arranged and antibiotic treatment should be started. When urgent microscopy is not available, a urine sample should be sent for microscopy and culture, and antibiotic treatment should be started.
If the symptoms are non-specific to UTI	For an infant or child with a high risk of serious illness: the infant or child should be urgently referred to a paediatric specialist where a urine sample should be sent for urgent microscopy and culture. Such infants and children should be managed in line with 'Feverish illness in children' (NICE clinical guideline 47). For an infant or child with an intermediate risk of serious illness: if the situation demands, the infant or child may be referred urgently to a paediatric specialist. For infants and children who do not require paediatric specialist referral, urgent microscopy and culture should be arranged. Antibiotic treatment should be started if microscopy is positive. When urgent microscopy is not available, dipstick testing may act as a substitute. The presence of nitrites suggests the possibility of infection and antibiotic treatment should be started. In all cases, a urine sample should be sent for microscopy and culture. For an infant or child with a low risk of serious illness: microscopy and culture should be arranged. Antibiotic treatment should only be started if microscopy or culture is positive.

Note: For urine microscopy, the cut-off of >10 WBC/HPF AND bacteria >10/HPF has the best diagnostic performance on ROC analysis by the GDG.

Table 4 Risk assessment of serious illness as defined in the "Fever Guidelines of NICE".[16]

High risk of serious illness (Red zone):
- Unable to arouse or if aroused does not stay awake
- Weak high-pitched or continuous cry
- Pale/mottled/blue/ashen
- Reduced skin turgor
- Bile-stained vomiting
- Moderate or severe chest indrawing
- Respiratory rate >60/min
- Grunting
- Bulging fontanelle
- Appearing ill to a healthcare professional
- Infants <3 months old with >38°C and infants aged 3-6 months old with >39°C should be recognised as high risk for serious illness

Intermediate risk of serious illness (Amber zone):
- Wakes only with prolonged stimulation
- Decreased activity
- Poor feeding in infants
- Not responding normally to social cues/no smile
- Dry mucous membranes

Table 5 Urine testing strategy for children 3 years or older. (Reproduced from the NICE Guideline,[15] with the permission of the Royal College of Obstetricians and Gynaecologists.)

Dipstick testing for leucocyte esterase and nitrite is diagnostically as useful as microscopy and culture, and can safely be used	
If both leucocyte esterase and nitrite are positive	The child should be regarded as having UTI and antibiotic treatment should be started. If a child has a high or intermediate risk of serious illness and/or a history of previous UTI, a urine sample should be sent for culture.
If leucocyte esterase is negative and nitrite is positive	Antibiotic treatment should be started if the urine test was carried out on a fresh sample of urine. A urine sample should be sent for culture. Subsequent management will depend upon the result of urine culture.
If leucocyte esterase is positive and nitrite is negative	A urine sample should be sent for microscopy and culture. Antibiotic treatment for UTI should not be started unless there is good clinical evidence of UTI (for example, obvious urinary symptoms). Leucocyte esterase may be indicative of an infection outside the urinary tract which may need to be managed differently.
If both leucocyte esterase and nitrite are negative	The child should not be regarded as having UTI. Antibiotic treatment for UTI should not be started, and a urine sample should not be sent for culture. Other causes of illness should be explored.

- If nitrite is positive in fresh urine, UTI is presumed and treatment should be started. One should also send urine culture to confirm the diagnosis.
- If only LE is positive, one should confirm by urine culture, and start treatment if culture is positive.
- If both LE and nitrite are negative, UTI can be excluded. Urine culture should be sent if child is still unwell after 24-48 hours.

4d. As in all diagnostic tests, there will be a small number of false negative results with the above strategy. Clinicians should use clinical criteria for their decisions in cases where urine testing does not support the clinical findings.

How Should the Acute Episode be Treated?

5a. Each patient should be assessed for risk factors for serious underlying pathology. These include poor urine flow, a history suggesting previous UTI or confirmed previous UTI, recurrent fever of unknown origin, antenatally diagnosed renal abnormality, family history of VUR or renal disease, constipation, dysfunctional voiding, enlarged bladder, abdominal mass, evidence of spinal lesion, poor growth, high blood pressure.

5b. Pyelonephritis/upper UTI is diagnosed if an infant or child has bacteriuria and fever >38°C and/or loin pain/tenderness. Cystitis/lower UTI is diagnosed in infants and children with bacteriuria but no systemic symptoms or signs. C-reactive protein alone should not be used to differentiate pyelonephritis from cystitis. Rarely pyelonephritis can be confirmed by power Doppler ultrasound or DMSA in the acute phase.

6a. Infants aged less than 3 months with a possible UTI should receive paediatric specialist care and be given parenteral antibiotics.

6b. For infants aged above 3 months with pyelonephritis, referral to specialists should be considered. They can be treated with oral antibiotics for 7-10 days, or if ill, with intravenous antibiotics and switched to oral treatment after response for a total duration of 10 days.

6c. For infants aged above 3 months with cystitis, they can be given oral antibiotics for 3 days, with reassessment at 24-48 hours for good response.

Other recommendations for acute treatment:

- Recommended intravenous antibiotics include cefotaxime or ceftriaxone. Oral antibiotics include cephalosporin or co-amoxiclav.
- Once-daily gentamicin or amikacin can be given.
- Intramuscular antibiotics are effective.
- For patients receiving prophylaxis, treatment should be with a different antibiotic.
- Asymptomatic bacteriuria should not be treated with antibiotics.
- Local laboratory should monitor resistance pattern of UTI pathogens to guide treatment in the local community.

Prevention of Recurrence

7a. Antibiotic prophylaxis should not be routinely recommended following first-time UTI. Antibiotic prophylaxis may be considered for recurrent UTI.

7b. Dysfunctional elimination syndrome and constipation should be treated.

7c. Adequate fluid intake should be encouraged.

7d. Children should have ready access to clean toilets and not delay voiding.

Imaging Strategy

8a. For infants aged below 6 months: an USG is recommended within 6 weeks if UTI is uncomplicated. For patients with atypical or recurrent UTI (as defined in Table 6), the full set of investigations should be performed, including USG (during the acute infection), MCUG AND DMSA (4-6 months after the infection) (see Table 7).

8b. For infants aged 6-36 months: No imaging is needed for uncomplicated UTI. For children with atypical or recurrent UTI, USG (urgent for atypical UTI, elective for recurrent UTI) AND DMSA (4-6 months after) are recommended. MCUG is considered if atypical or recurrent UTI AND a) if pelvic dilatation is shown on USG or b) patient has poor urine flow or c) non-E.coli UTI or d) a family history of VUR (see Table 8).

8c. For children aged >3 years: No imaging is needed for uncomplicated UTI. USG is recommended for atypical UTI. USG and DMSA scan are recommended for patients with recurrent UTI (see Table 9).

Surgical Intervention for VUR

9. Surgical management of VUR is not routinely recommended.

Follow Up Strategy

10a. Infants and children who do not undergo imaging should not routinely be followed up.

10b. If imaging is done and normal, parents should be informed in writing and patients do not need follow up.

10c. Patients with recurrent UTI or abnormal imaging results should be referred to paediatricians. Assessment includes body weight, body height, blood pressure (BP), and test for proteinuria.

10d. Patients with minor unilateral renal parenchymal defect do not need long-term follow up unless they have recurrent UTI or family history or lifestyle risk factors for hypertension.

10e. Patients with bilateral renal abnormalities, impaired kidney function, raised BP, or proteinuria need monitoring and management by nephrologists to slow progression of chronic kidney disease.

10f. Patients who are asymptomatic should not routinely have urine re-tested for infection.

10g. Asymptomatic bacteriuria is not an indication for follow up.

Table 6 Definitions of atypical and recurrent UTI. (Reproduced from the NICE Guideline,[15] with the permission of the Royal College of Obstetricians and Gynaecologists.)

Definition of atypical UTI:
• Seriously ill ("red" zone in Fever Guideline, Table 4)
• Poor urine flow
• Abdominal or bladder mass
• Raised serum creatinine
• Septicemia
• Failure to respond to treatment with suitable antibiotics within 48 hours
• Infection with non-E.coli organisms
Definition of recurrent UTI:
• Two or more episodes of UT with acute pyelonephritis/upper UTI, or
• One episode of acute pyelonephritis/upper UTI plus one or more episodes of cystitis/lower UTI
• Three or more episodes of cystitis/lower UTI

Table 7 Recommended imaging schedule for infants younger than 6 months. (Reproduced from the NICE Guideline,[15] with the permission of the Royal College of Obstetricians and Gynaecologists.)

Test	Uncomplicated UTI, responds well to treatment within 48 hours	Atypical UTI[a]	Recurrent UTI[a]
Ultrasound during the acute infection	No	Yes[c]	Yes
Ultrasound within 6 weeks	Yes[b]	No	No
DMSA 4-6 months following the acute infection	No	Yes	Yes
MCUG	No	Yes	Yes

Note: [a]See Table 6 for definition.

[b]If USG abnormal, consider MCUG.

[c]If an infant or child with a non-E.coli UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks.

Table 8 Recommended imaging schedule for infants and children 6 months or older but younger than 3 years. (Reproduced from the NICE Guideline,[15] with the permission of the Royal College of Obstetricians and Gynaecologists.)

Test	Uncomplicated UTI, responds well to treatment within 48 hours	Atypical UTI[a]	Recurrent UTI[a]
Ultrasound during the acute infection	No	Yes[c]	No
Ultrasound within 6 weeks	No	No	Yes
DMSA 4-6 months following the acute infection	No	Yes	Yes
MCUG	No	No[b]	No[b]

Note: [a]See Table 6 for definition.

[b]While MCUG should not be performed routinely, it should be considered if the following features are present:

- Dilatation on ultrasound
- Poor urine flow
- Non-E.coli infection
- Family history of VUR

[c]If an infant or child with a non-E.coli UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks.

Table 9 Recommended imaging schedule for children 3 years or older. (Reproduced from the NICE Guideline,[15] with the permission of the Royal College of Obstetricians and Gynaecologists.)

Test	Uncomplicated UTI, responds well to treatment within 48 hours	Atypical UTI[a]	Recurrent UTI[a]
Ultrasound during the acute infection	No	Yes[b,c]	No
Ultrasound within 6 weeks	No	No	Yes[b]
DMSA 4-6 months following the acute infection	No	No	Yes
MCUG	No	No	No

Note: [a]See Table 6 for definition.

[b]Ultrasound in toilet-trained children should be performed with a full bladder with an estimate of bladder volume before and after micturition.

[c]If an infant or child with a non-E.coli UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a non-urgent basis to take place within 6 weeks.

Discussion

The authors agree that the guideline has been developed through a stringent process and accepted that it truly represent the current state of knowledge in this area. The Guideline report contained narrative summaries of the retrieved studies, based on which the GDG made interpretations and recommendations. The key recommendations were not explicitly graded by levels of recommendations or evidence. The authors also appreciate the expert opinions of the GDG where firm evidence is lacking.

Diagnosis

The diagnostic algorithm is reasonable especially for primary care doctors. Clean catch urine is always the recommended non-invasive collection method which can be successful even in infants if parents are skilful. However in the busy hospital practice, suprapubic aspiration and bladder catheterisation are sometimes needed to rapidly collect a proper urine sample before starting antibiotic therapy for the sick patient. It is also noteworthy that urine microscopy as described in the Guideline includes examination for leucocytes and Gram's stain for bacteria, so local laboratories should develop this service to conform to the Guideline.

The Guideline provides convincing statistical evidence that bedside tests (urine microscopy for <3-year-old and dipstix for >3-year-old children) can practically rule in and rule out UTI for the purpose of starting treatment. However, for confirmation of diagnosis, the Guideline also recommends urine culture in the <3-year-old children. One drawback is that it does not discuss the criteria of colony counts to diagnose UTI, as in previous guidelines.[2] The GDG considered that a positive urine culture should not be interpreted in isolation, but should be interpreted in relation to the clinical setting, symptoms and findings, and other diagnostic tests (see page 53 of Guideline). This is because counts as low as 1000 CFU/ml or mixed growth can, in certain unusual clinical situations, represent a true UTI. It is the authors' experience that in this age group, especially in uncircumcised male infants, clinical symptoms and bedside urinalysis have frequent false-positives, and culture results in terms of colony counts and pure/mixed growths can help to increase or decrease the probability of UTI.[17]

On the other hand, the Guideline does not recommend urine culture for >3-year-old children if both dipstix for nitrite and leucocyte esterase are positive, except when clinical response to treatment is unsatisfactory, or there is recurrent UTI. The authors wish to point out that a pre-treatment culture is valuable in identifying the bacteria and its antibiotics sensitivity. When there is poor response to treatment, the chance of identifying the organism will have been lost, and there is no way to distinguish inadequate or inappropriate antibiotic therapy or other reasons for poor response.

Acute Treatment

The NICE Guideline distinguishes between treatment for upper and lower UTI. However, there is uncertainty in clinically distinguishing upper and lower UTI in young children. The recommendation of short course treatment is only applicable for the older child who is afebrile and has only cystitis symptoms.

In contrast to previous guidelines, the NICE Guideline allows ambulatory care with oral antibiotic therapy for stable infants aged >3 months. Before doing this, the doctor has to ensure that the parents or caretakers are competent to observe for any signs of deterioration, and that a follow up appointment for re-assessment of the patient can be arranged in 24-48 hours.

Strategy of Further Imaging and Antibiotic Prophylaxis

One of the major differences between the NICE Guideline and previous guidelines is the much more selective recommendations for imaging after a first-time UTI and its recommendation against prophylactic antibiotics for VUR.

The recommendations concerning USG were based on studies by Hoberman et al[11] and Zamir et al[18] which showed that USG detected only minor abnormalities in 12 to 14% of patients respectively and they did not alter the management. These studies however had excluded patients already known to have urological abnormalities. Naturally the yield of USG was low in such a selected patient population. This may be applicable to societies with good/universal antenatal USG service which would have detected most urological abnormalities before the patients develop UTI. However, it is uncertain whether this is also applicable in other societies. Giorgi et al reported that in their cohort of 282 patients, USG detected conditions that required a change in management in 9 cases.[19] We need local studies to confirm whether any significant urological cases will be missed with this imaging strategy. In the meantime, since USG is noninvasive and the early detection of even a small number of obstructive uropathy would be worthwhile, it is reasonable to recommend USG after a first time UTI if no reliable USG had been done before.

Concerning MCUG and antibiotic prophylaxis for VUR, the NICE Guideline was based on the arguments that MCUG was invasive, that VUR was only a weak predictor of renal scarring;[12] and that even if VUR was present, its treatment with antibiotics prophylaxis was not beneficial.[13] The Guideline quoted a randomised control trial (RCT) of antibiotic prophylaxis in children with VUR Grade I to III by Garin et al who compared 55 children on prophylaxis versus 58 children on no treatment. They found no difference in the rates of recurrent symptomatic UTI or renal scarring between the groups.[13] Since the publication of the NICE Guideline, two more RCTs were published (Table 10). A French multicentre RCT, on 225 children with Grade I to III VUR, also showed no significant difference in overall UTI recurrence rates in prophylaxis versus no treatment group. However, post-hoc analysis showed benefit of prophylaxis in boys with Grade III VUR.[20] An Italian RCT involving 100 children with Grade II to IV VUR confirmed the absence of benefit of prophylaxis in recurrent UTI or renal scarring.[21] Though there might be criticisms on their statistical power, absence of placebo, uncertainties of drug compliance and UTI diagnosis, these studies confirmed that antibiotic prophylaxis was not beneficial for Grade I-III VUR. The value of prophylaxis, or the best treatment, for Grade IV-V VUR is however undecided. Indeed, a larger multicentre RCT (the RIVUR Study) including these patients is currently ongoing in North America.[22] It is reasonable for the GDG not to recommend a management strategy (that is, to do MCUG to detect Grade IV-V VUR and give antibiotic prophylaxis) that has no proven value. The main risk of this strategy is missing Grade IV-V VUR, but the risk is considered small in children without high-risk clinical features (as shown in Table 6) and normal USG scan. Nevertheless further studies are needed to confirm this assumption. In the meantime parents need to be informed of the slight possibility of missing severe VUR for which antibiotic prophylaxis may or may not be beneficial. The parents' preference for prophylactic antibiotics for Grade IV-V VUR needs to be taken into consideration in clinical decision making.

Follow Up Strategy

The NICE Guideline is thorough in defining who needs long term follow up and who does not. However, the term "minor unilateral DMSA defects" is not well defined. It is commented that the long term significance of persistent DMSA defects is "unknown" (see page 110 of Guideline). This is not equivalent to "unimportant" and longer term studies are needed.

Conclusion and Recommendations

The management of childhood UTI is always in the process of evolution. The NICE Guidelines has incorporated recent scientific findings but made some recommendations from extrapolation of current limited evidence. Its highly selective imaging strategy is undoubtedly a major swing of the pendulum, and has ignited discussion as shown in several commentaries, all of which did not agree or disagree but pointed out that further studies are needed.[22-24] For some prudent clinicians, a more gradual change based on current evidence may be more appropriate.

It is not our purpose to replace entirely the NICE Guideline, but until more data are available, the authors would recommend the following modifications, or options, for parents to consider:

1. Sending a proper urine sample for culture in >3-year-old patients who are sick enough to be hospitalised, to identify the causative organism and its antibiotic susceptibility.
2. Considering the symptoms, signs, urinalysis results AND culture (pure/mixed growth and colony counts) in making a diagnosis of UTI in children.
3. Doing an USG scan after a first UTI in a young child, if he or she has not had a reliable antenatal or postnatal USG screening.
4. Discussing with parents, for children below 3 years with first UTI, about the role of MCUG. Following the NICE Guideline is a reasonable option, if parents accept the small risk of missing severe VUR (Grade IV-V) for which antibiotic prophylaxis or other treatment options may or may not be beneficial. However, if parents accept the risk of the imaging studies, the following may be a more prudent approach: For infants below 12 months, we recommend USG, MCUG (as early as feasible after infection is controlled) and DMSA (at 6 months). For children aged 12 to 36 months, we recommend doing USG and DMSA (at 6 months), plus MCUG if the patient has recurrent UTI, poor urine stream, family history of VUR, dilatation found on USG or scarring on DMSA.
5. Discussing with parents about the role of antibiotic prophylaxis, mentioning the evidence of no benefit in most patients with Grade I-III VUR (except boys with Grade III VUR) but the lack of studies in Grade IV-V VUR. Parents should be counselled and offered antibiotic prophylaxis for Grade IV-V VUR if they prefer.
6. Cautioning parents about the importance of recognising

Table 10 Summary of RCT of effects of antibiotics prophylaxis versus no treatment on symptomatic UTI and renal scarring in children with VUR

References	Study design	Patient selection and treatment	Quality assessment	Results	Remarks
Garin et al, USA, 2006[13]	RCT; central randomisation; stratified by VUR Grade (Gd)	236 patients, aged 3 m-18 y (Treatment vs Control) No VUR – 45 vs 60 VUR Gd I – 9 vs 10 Gd II – 28 vs 29 Gd III – 18 vs 19 Compared co-trimoxazole or nitrofurantoin versus no drug for 12 months	Adequate power: assume risk 30% in control, detect difference of 20% Compliance: not mentioned Outcome assessment: by Cath or CCU urine dipstix+culture 3 monthly and when symptoms+; DMSA at 6 m post UTI	No differences in Treatment vs Control Groups – Rate of recurrent UTI: No VUR: cystitis 2.2% vs 13.8%; Pyelonephritis 4.5% vs 3.3% With VUR: cystitis 9.2% vs 15.5%; Pyelonephritis 12.9% vs 1.7% Rate of renal scars: No VUR: 4.5% vs 6.6% With VUR: 9% vs 3.4%	All recurrent UTI organism resistant to antibiotic used
Roussey-Kesler et al, French, 2008[20]	RCT; central randomisation; stratified by gender, VUR Grade (Gd)	225 patients, aged 1 m-3 y, boys uncircumcised (Treatment vs Control) VUR Gd I – 8 vs 14 Gd II – 70 vs 77 Gd III – 24 vs 30 Compared co-trimoxazole vs no drug for 18 months	Adequate power: assume risk 30% in control, detect difference of 20% Compliance: not mentioned (In treatment group, 27% of recurrence by organism sensitive to co-trimoxazole, ? non-compliant) Outcome assessed by: bag or CCU for dipstix+ culture monthly or when symptoms+; DMSA at 4-6 months post UTI recurrence	Treatment vs Control Total UTI: 17% vs 26% Febrile UTI: 13% vs 16% No difference by survival analysis for whole group; but significant difference for boys with p=0.013 (all Gd) and 0.04 (Gd III).	Default cases considered as censored
Pennesi et al, Italy, 2008[21]	Central randomisation; stratified by gender, age, VUR Grade (Gd)	100 patients, aged 1 m-30 m (Treatment vs Control) VUR Gd II - 11 vs 10 Gd III – 22 vs 24 Gd IV – 17 vs 16 Compared co-trimoxazole vs no drugs for 2 years, observed for 4 years	Adequate power if assume risk of 60% in control and detect difference of 30% Compliance ensured by testing urine for antibiotics at UTI recurrence Outcome assessed by: fever and Cath or CCU for RM+Culture; DMSA at 2 years post UTI	(Treatment vs Control Group) Risk of recurrent UTI: RR 1.2 (95%CI 0.68-2.11) – same for each VUR Grade Scars on DMSA: 40% vs 36% VUR persistence at 4 years: same rate	UTI organisms: In Treatment Gp: Variable & multiresistant In Control Gp: all E.coli, sensitive to all antibiotics

recurrence of UTI, to seek early treatment and to proceed to imaging studies as recommended by the Guideline.

Furthermore, certain logistic issues in our local health care system need to be addressed before clinicians can fully comply with the NICE Guideline:

7. Urine microscopy for Gram stain for bacteria should be available as an emergency laboratory service.
8. The current waiting list for imaging studies in some public hospitals cannot cope with the time limits of doing ultrasound (4-6 weeks), DMSA (4-6 months) and MCUG as specified by the NICE Guideline.
9. According to the Guideline, certain children seen at primary care setting or Accident and Emergency Departments will be discharged home pending reassessment after 24 hours (febrile children with a focus of infection – urine should be tested if patient is still unwell after 24 hours) or 48 hours (children diagnosed as UTI and given ambulatory treatment – response has to be assessed at 48 hours). Thus a system to ensure follow up of these patients should be in place at the Accident and Emergency Departments or General outpatient clinic.
10. With the current practice of doctor shopping by patients rather than following one family doctor as in the NHS system in the UK, it may be difficult to monitor children for recurrence of UTI, resulting in missing children at high risk of urological abnormalities and progressive renal damage.

It is also recommended that paediatric nephrology colleagues should do collaborative studies:

1. To estimate the chance of missing significant renal abnormalities if the NICE Guideline is followed in the local population; and
2. To study the efficacy of antibiotics prophylaxis in severe grades of VUR; and
3. To monitor serially the uropathogens in children and their antibiotic resistance pattern.

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