Clinical Guideline

Clinical Guideline on Management of Urinary Tract Infections in Children below 2 Years of Age (Part I): The Diagnosis and Initial Management

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Foreword

This Guideline had been developed by Quality Assurance Sub-committee, COC in Paediatrics and the expert authors for the Hospital Authority according to the state of medical knowledge at the time of publication. It has been established that doctors can act in accordance with a practice accepted as proper by a responsible body of medical opinion even though others may adopt a different practice. As such, this guideline is for general guidance only; the management of individual cases must be the clinical judgment and decision of the medical practitioners after considering all relevant circumstances, information and up-to-date medical knowledge. In view of the general nature of this guideline and the changes in medical science, the Hospital Authority, the Paediatric COC and the authors do not assume or accept any liability for this guideline.

Explanatory Notes on Level of Evidence and Grading System on Recommendation

The definition of types of evidence and grading recommendations originate from the US Agency for Health Care Policy and Research (AHCPR) and are also recommended and used by the Royal College of Paediatrics and Child Health.

Levels of evidence

Level	Type of evidence (based on AHCPR 1992)
Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grading of recommendations

Level	Type of recommendation (based on AHCPR 1994)
A (Levels Ia, Ib)	Requires at least one randomised control trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (Levels IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation
C (Level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality

Evidence is graded upon the methodological qualities. Guidelines normally contain many different recommendation based upon different levels of evidence. It is important that users are aware of the level of evidence on which each guideline recommendation is based. The link between guideline recommendation and the supporting evidence should be made explicit. Separating the strength of the recommendation from the level of evidence helps in situations where extrapolation is required to take the evidence of a methodologically strong study and apply it to the target population. Gradings of recommendation in addition to level of evidence allow more flexibility for future revision. However, it is important to emphasis that the grading does not relate to the importance of the recommendation.

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Summary of recommendation

Recommendation

The diagnosis of UTI should be considered in any child aged younger than 2 years with documented fever but no identifiable focus of infection.
(Level III Evidence, Grade B Recommendation)

Urine examination to exclude UTI may need to be considered in the following situations:
- Unexplained vomiting or abdominal pain
- Failure to thrive
- Non-specific illness
- Suspected sexual abuse
- Haematuria or hypertension

(Level IV Evidence, Grade C Recommendation)

The diagnosis of UTI should be proven by a positive bacterial culture from a properly collected urine sample. The diagnostic criteria of different collection methods are shown in Table 1.
(Level IV Evidence, Grade C Recommendation)

Diagnostic strategies
- In sick patients who are judged by the clinician to require immediate initiation of antibiotic therapy, urine should be collected either by suprapubic aspiration or by catheterisation (plus other investigations, e.g. blood and CSF cultures, renal function tests, as appropriate) before antibiotics commencement.
- For patients who do not require immediate antibiotic therapy, urine can be collected by a non-invasive method (e.g. bag, clean-catch) and tested by leucocyte esterase, nitrite, and microscopy. Any positive test results indicate the need to collect a proper urine sample for culture (preferably suprapubic tap or catheterised urine, though proper clean-catch urine is also acceptable). Another acceptable option is to obtain urine by suprapubic tap or catheterisation or clean catch method for culture for all patients in this group. In either option, antibiotic therapy is commenced if urinalysis of the properly collected sample also yields positive results, while culture results are awaited.

(Level III Evidence, Grade B Recommendation)

Treatment strategies:
Admission to hospital is indicated for all young patients with proven UTI. They may be toxic, vomiting or dehydrated, and require immediate treatment with intravenous fluid and antibiotics. The choice depends on local antibiotics susceptibility patterns.
(Level IV Evidence, Grade C Recommendation)

Treatment strategies:
Antibiotic should be given for at least 7 days.

For patients older than one month and provided compliance can be ensured, it is possible to switch to oral therapy and outpatient management once fever has subsided.
(Level Ib Evidence, Grade A Recommendation)

Patients with UTI who do not show the expected clinical response to antibiotics therapy should have urine re-cultured. The co-existence of septicaemia and meningitis should be considered, and ultrasound kidneys should be performed on an urgent basis. Surgical intervention may be indicated for unresolved urosepsis if obstructive hydronephrosis or complicated malformations are present.
(Level IV Evidence, Grade C Recommendation)

Special caution is needed to apply this guideline to the neonates –
- Among neonates investigated for sepsis in the first 3 days of life, the incidence of UTI was very rare. Urine culture is not routinely included as part of sepsis workup in the first 3 days of life[21]
- In one case series, half of the patients younger than 8 weeks with documented UTI have negative urinalysis results. Therefore culture of a properly collected urine sample is an essential part of evaluation of fever in this age group.[22]

(Level IV Evidence, Grade C Recommendation)

Table 1   Diagnostic criteria for UTI (based on Hellerstein[9])

Method of collection	Colony count per ml (pure culture)	Probability of infection (%)
Suprapubic tap	Gram-negative bacilli: any number	>99%
	Gram-positive cocci: >a few thousand	>99%
Transurethral catheterisation	$>10^5$	95%
	10^4-10^5	Infection likely
	10^3-10^4	Suspicious, repeat
	$<10^3$	Infection unlikely
Clean-voided urine		
Boys	$>10^4$	Infection likely
Girls	3 specimens $>10^5$	95%
	2 specimens $>10^5$	90%
	1 specimen $>10^5$	80%
	5×10^4-10^5	Suspicious; repeat
	1×10^4-5×10^4	If symptomatic – suspicious, repeat
		If asymptomatic – infection unlikely
	$<10^4$	Infection unlikely

Introduction

Urinary tract infection (UTI) is probably one of the most controversial paediatric nephro-urological problem. It is a common childhood infection affecting about 5% of children.[1] It is important because it is believed to cause permanent renal damage, particularly if treatment is delayed. A survey by the Royal College of Paediatrics and Child Health revealed that there are wide variations in the practice of diagnosis and management of this problem.[2]

This Panel was commissioned by the QA Subcommittee to study the literature and propose practice guidelines through a multi-specialty approach so that it can be accepted as the recommended practice by generalists, paediatricians, radiologists, and urologists.

There are still many unresolved clinical issues in UTI, and in light of new evidence, it is expected that the investigation and treatment are likely to change drastically in the near future. Therefore, this first Guideline will only focus on the standard of diagnosis of UTI in young children and its acute management. It should be stressed that diagnosis should be properly documented because false positive diagnosis leads to unnecessary invasive investigations, while false negative diagnosis leads to missed or delay in treatment with risk of renal damage or even disseminated sepsis.

In formulating our recommendations, we have referred heavily to the data provided by several recent reviews and guidelines published by the American Academy of Pediatrics (AAP),[1,3] Royal College of Physicians,[4] and the Swedish Medical Research Council.[5] It is however also important to consider the acceptability by the local community.

In accordance of recommendations from the Quality Assurance Subcommittee, we have categorised the levels of evidence and grades of recommendation as based on AHCPR 1992 and RCPCH.

Background Information about UTI[6]

UTI refers to the presence of proliferating bacteria in the urinary tract. It is common in both sexes in the first year of life, but thereafter it commonly affects girls. Although UTI can be distinguished into pyelonephritis or cystitis in adults and older children, all young febrile children with UTI are considered as having pyelonephritis. The pathogenesis is multifactorial but involves the invasion of the urinary tract by a virulent bacteria mainly from the gut flora which overcomes the host defence mechanism. *Escherichia coli* accounts for 75% of all pathogens isolated, followed by *Proteus* species (especially in boys), other Gram-negative bacteria and *Enterococcus*.

The significance of UTI is that: 1) It frequently recurs. Even with antibiotic prophylaxis, the overall recurrence rate of symptomatic UTI was 15% in girls and in male infants.[7] 2) UTI may signal the presence of an underlying urological

abnormality or vesicoureteric reflux in the patient, and 3) It may lead to permanent renal scarring with its long term consequences. The risk of renal scarring was positively associated with the severity of VUR and number of recurrent febrile UTI. Long term studies showed that ESRD develops in 3-10% of patients with extensive scarring.[1]

Recommendations: 1. ***The diagnosis of UTI should be considered in any child aged younger than 2 years with documented fever but no identifiable focus of infection.***

(Grade of Recommendation: B)
(Level of Evidence: III)

Note:
- The baseline risk of UTI was derived from a meta-analysis of case series by the AAP showing that the pooled prevalence of UTI among febrile children aged 3 months to 2 years was 5%.[1]
- A cross-sectional study of febrile children younger than 12 months attending emergency department showed an overall prevalence of 3.3%. Prevalence was increased with the following risk factors: absence of source of fever (5.9% vs 2.7%, p<0.001), ill looking (5.7% vs 2.4%, p<0.001), any urinary symptoms (8.6% vs 3.2%, p<0.04), uncircumcised state (8.0% vs 1.2%, p<0.002), abdominal tenderness (13.2% vs 2.2%, <0.02), previous history of UTI (9.3% vs 3.2%, p<0.03).[8]

Recommendations: 2. ***Urine examination to exclude UTI (with the following strategy) may need to be considered in the following situations:***
  - ***Unexplained vomiting or abdominal pain***
  - ***Failure to thrive***
  - ***Non-specific illness***
  - ***Suspected sexual abuse***
  - ***Haematuria or hypertension***

(Grade of Recommendation: C)
(Level of Evidence: IV)

Note:
- Based on the recommendation by expert panel from Royal College of Physicians.[4]

Recommendations: 3. ***The diagnosis of UTI should be proven by a positive bacterial culture from a properly collected urine sample. The diagnostic criteria of different collection methods are shown in Table 1.***[9]

(Grade of Recommendation: C)
(Level of Evidence: IV)

Note:
- Tap urine cultures was considered to be the "gold-standard". It is the preferred method in infants below 1 year old. Contra-indications of suprapubic tap should be observed (generalised bleeding tendency, infection of suprapubic skin).
- For the other collection methods, contamination may occur and diagnosis depends on the quantitative colony counts to distinguish between contamination and genuine infection. The criteria in Table 1 was first proposed by Hellerstein in 1982 and adopted by most guidelines and clinical studies to define UTI, although they are based on expert opinion only. It is also important to send any urine sample to laboratory for plating immediately and arrange for the laboratory to report the colony counts rather than just the microorganism in the culture report.
- Catheter collection is a sure way to obtain a urine sample immediately before starting antibiotic therapy. However, the diagnostic criteria was controversial. The AAP review concluded that if the cultures yielding >1000 colony forming units/ml are considered positive, it has a 95% sensitivity and 99% specificity.[1] However they also cautioned the reader about the problem of contamination. In doubtful scenarios, especially when CSU yields any counts >10^3 cfu/ml in uncircumcised males, or borderline counts of 10^3-10^4 cfu/ml in females or circumcised males, a repeat culture preferrably of suprapubic aspirated urine should be obtained if possible. However if there is no chance to repeat, e.g. patient has already been given antibiotic therapy, UTI is likely if the clinical picture is suggestive. In case establishment of a firm diagnosis is strongly desired, an early DMSA scan can confirm the presence of acute pyelonephritis.
- The clean-catch urine has the advantage of being non-invasive but the disadvantages of being more time- and effort-consuming. The same problem of contamination as discussed above also applies to clean-catch urine samples.

- Bag urine cultures should be discouraged because of its low specificity (14-84%).[1]

Recommendations: 4. Diagnostic strategies

A. In sick patients who are judged by the clinician to require immediate initiation of antibiotic therapy, urine should be collected either by suprapubic aspiration or by catheterisation (plus other investigations, e.g. blood and CSF cultures, renal function tests, as appropriate) before antibiotics commencement.

B. In patient who do not require immediate antibiotic therapy, urine can be collected by a non-invasive method (e.g. bag, clean-catch) and tested by leucocyte esterase, nitrite, and microscopy. Any positive test results indicate the need to collect a proper urine sample for culture (preferrably suprapubic tap or catheterised urine, though proper clean-catch urine is also acceptable). Another acceptable option is to obtain urine by suprapubic tap or catheterisation or clean catch for culture for all patients in this group. In either option, antibiotic therapy is commenced if urinalysis of the properly collected sample also yield positive results, while culture results are awaited.

(Grade of Recommendation: B)
(Level of Evidence: III)

Note:
- Delayed treatment of febrile UTI was associated with increased rates of renal scarring. In a retrospective analyses of 52 children with renal scarring associated with reflux and UTI, 41 had delay in diagnosis (defined as high fever lasting for at least 5 days), and 45 had delay in starting treatment (defined as more than 4 days from the collection of urine to the start of effective treatment).[10] In the piglet model of UTI and VUR by Ransley and Risdon, 33% and 68% of the at-risk renal parenchyma already had inflammatory damage and/or scarring if UTI persisted for 1 week and 2 weeks respectively.[11]

- Two meta-analyses on the test characteristics of bedside urinalysis for UTI were reported by the AAP[1] and Gorelick and Shaw.[12] This has been summarised by Moyer et al. in Table 2.[13] A parallel combination of microscopy for leucocytes and bacteria, plus leucocyte esterase plus nitrite has a mean sensitivity of 99.8% (range 99-100%) and a mean specificity of 70% (range 60-92%). It must be pointed out that these results were obtained in studies using careful techniques in on-site laboratories and fresh urine samples.

- A risk analysis and cost effectiveness analysis for diagnosis and treatment of UTI was reported by the AAP involving the following options:
  1) treat all cases without testing;
  2) culture all by catheterisation and suprapubic tap;
  3) culture all by bag urine;
  4) urinalysis for all;
  5) urinalysis for all and culture positive cases;
  6) observe all without treatment.
  The results suggest that options (2) and (5) have the lowest incidence of adverse outcomes e.g. hypertension, ESRD and deaths, while option (5) has slightly less cost.[1] Two other cost-benefit analysis reported similar recommendations.[14,15]

- Culture of clean-voided urine is acceptable for establishing diagnosis of UTI (see recommendation 3). We must be aware of the possible delay in its collection and in starting antibiotic therapy, and the risk of contamination. In actual practice, many infants void when the suprapubic area is sterilised before suprapubic tap, we should be prepared to collect the clean-voided urine.

- In case UTI is considered unlikely from the initial urinalysis, the clinical course of the patient should be followed. The diagnosis of UTI need to be reconsidered if there is persistent fever with no other explanation.

Recommendations: 5. Treatment strategies:

A. Admission to hospital is indicated for all young patients with proven UTI. They may be toxic, vomiting or dehydrated, and require immediate treatment with intravenous fluid and antibiotics.

Table 2   Characteristics of bedside urinalysis tests for UTI

Tests	Sensitivity (%)	Specificity (%)	Range of positive likelihood ratios#
WBC seen on microscopy:			
>5/hpf (centrifuged)	73*; 79^	81*; 67^	2.5-3.9
>10/mm^3 (uncentrifuged)	77^	89^	7
Gram stain, any organisms	93^	95^	18.6
Bacteria seen on microscopy	81*	83*	4.8
Leukocyte esterase (LE) +ve	83*; 83^	78*; 84^	3.8-5.2
Nitrite +ve	53*; 50^	98*; 98^	25-26.5
Nitrite or LE +ve	93*; 88^	72*; 93^	3-13.3
Nitrite, LE, or microscopy for WBC +ve	99.8*	70*	

Source: *AAP technical report;[1] ^Gorelick and Shaw;[12] #Moyer and Craig[13]

The choice depends on local antibiotic susceptibility patterns.

(Grade of Recommendation: C)
(Level of Evidence: IV)

B. *Antibiotics should be given for at least 7 days.*

(Grade of Recommendation: A)
(Level of Evidence: Ib)

Note:
- Moffat et al. reviewed 14 RCTs comparing short course (ranging from single dose to 4 days) versus conventional treatment (range: 7-10 days). Two studies showed that short courses had lower cure rate than conventional treatment (In one study, amoxil single dose was compared to standard course: cure rates were 63% versus 92%, p<0.01. In the second study, cefadroxil one day was compared to standard course: cure rates were 56% versus 80%, p<0.05). The remaining 12 studies that found no difference in cure rates did not recruit sufficient numbers of patients to avoid false-negative β errors.[16]
- The AAP review found seven studies with 10 comparisons between long duration (7 to 10 days) and short duration (one dose to 3 days) for amoxicillin, septrin, cefodroxil and pipemidic acid, 8 of the 10 comparisons showed better results for long duration regimens, with an attributable improvement in outcome of 5% to 21%.[1]
- No RCTs were found comparing 5-day courses of antibiotics with other regimens.[17] There was no data on comparison of 7-day courses versus 14-day courses. As

commented in the AAP guideline, many experts prefer 14 days for ill-appearing children with clinical evidence of pyelonephritis.[1,3]
- Aminoglycosides, second or third generation cephalosporins are reasonable first-line drugs for intravenous treatment. Cefuroxime axetil and co-trimoxazole are reasonable first-line alternative for oral treatment. Nitrofurantoin and nalidixic acid which cannot achieve adequate blood levels should not be used in febrile infants in whom renal involvement is likely. Septrin, nitrofurantoin, nalidixic acid are not recommended for infants aged 3 months or younger.[3]

Recommendations: 5.   Treatment strategies:
C. For patients older than one month and provided compliance can be ensured, it is possible to switch to oral therapy and out-patient management once fever has subsided .

(Grade of recommendation: A)
(Level of evidence: Ib)

Note:
- Based on the AAP recommendation. The AAP review did not find any data comparing oral and parenteral therapy.
- One valid RCT of 306 febrile children with UTI aged 1 month to 2 years treated with either 14 days of oral cefixime or 3 days of iv cefotaxime followed by 11 days of oral cefixime showed no significant difference in outcomes (mean time until afebrile, symptomatic reinfection rates, rates of renal scarring at 6 months), but less cost with oral treatment.[18]

- An RCT involving 220 patients with acute pyelonephritis aged 3 months to 16 years comparing 10 days versus 3 days of intravenous ceftriaxone followed by oral cefixime to complete a 15-day course showed no significant difference in rates of renal scarring at 3 months or recurrent UTI.[19]

Recommendations: 6. ***Patients with UTI who do not show the expected clinical response to antibiotics therapy should have urine re-cultured. The co-existence of septicaemia and meningitis should be considered, and ultrasound kidneys should be performed on an urgent basis. Surgical intervention may be indicated for unresolved urosepsis if obstructive hydronephrosis or complicated malformations are present.***

(Grade of Recommendation: C)
(Level of Evidence: IV)

Note:
- Recommendation by expert panel.[1,3]
- In one retrospective review of 288 children below 2 years old with UTI, 68% were afebrile by 24 hours after antibiotic therapy and 89% by 48 hours.[20]
- It was considered not necessary to repeat urine culture during treatment for uncomplicated UTI. However, a repeat culture should be performed after 48 hours of treatment if the patient does not show the expected clinical response, or if the sensitivity of the micro-organism to the chosen antibiotic is determined to be intermediate or resistant, or if sensitivity test is not performed.[1,3]

Recommendations: 7. ***Special caution is needed to apply this guideline to the neonates –***
   A. Among neonates investigated for sepsis in the first 3 days of life, the incidence of UTI was very rare. Urine culture is not routinely included as part of sepsis workup in the first 3 days of life.[21]

   B. In one case series, half of the patients younger than 8 weeks with documented UTI have negative urinalysis results. Therefore culture of a properly collected urine sample is an essential part of evaluation of fever in this age group.[22]

Acknowledgement

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