HK J Paediatr (new series) 2003;**8**:47-54

Clinical Guideline

Clinical Guideline on Management of Urinary Tract Infections in Children below 2 Years of Age (Part II): Investigations Following a Documented Infection

SN ***Wong,*** W ***Chiu,*** S ***Ho,*** PW ***Ko,***
W ***Lam,*** CK ***Yeung,*** MC ***Chiu,*** CS ***Ho,*** W ***Wong***

Guideline Development Panel

Dr. SN Wong (Chairman)
Dr. W Chiu (Coordinator)
Dr. S Ho
Dr. PW Ko
Dr. W Lam
Prof. CK Yeung

Guideline Review Panel

Dr. MC Chiu
Dr. CS Ho
Dr. W Wong

Date of Endorsement 1st November, 2002

Date of Review 1st November, 2004

Quality Assurance Subcommittee Co-ordinating Committee in Paediatrics Hospital Authority

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.

The Follow-up Investigations and Management of Urinary Tract Infections in Children below 2 years of age

Summary of recommendation

Recommendation

Follow-up investigations are directed to detect underlying anatomical abnormalities of the urinary tract and vesicoureteric reflux (VUR), to assess renal functions and degree of scarring of each kidney, and to look for bladder dysfunction.

Follow-up management are directed to prevent, detect and treat any recurrent UTI, to manage any urological abnormalities appropriately, and hence prevent further renal scarring and its long term sequalae.

(Level II Evidence, Grade B Recommendation)

Clinical assessment should include inquiry into bowel and bladder habits, documenting signs of chronic renal failure, hypertension, palpable kidneys and bladder, lumbosacral spinal abnormalities, weak urine stream, and serum creatinine level. In children with any abnormalities, the schedule for follow up investigations should be accelerated.

(Level IV Evidence, Grade C Recommendation)

A prophylactic antibiotic should be given to cover the period while waiting for investigations. It can be stopped if significant vesicoureteric reflux and obstructive uropathy are ruled out.

(Level IV Evidence, Grade C Recommendation)

It is important that the family be educated to recognise the symptoms and signs of recurrent UTI, and be advised to seek immediate medical care when UTI is suspected. It is mandatory to check for UTI recurrence when the diagnosis is suspected. It is optional to test urine microscopy and culture regularly every 3 months.

(Level IV Evidence, Grade C Recommendation)

It is strongly recommended to do ultrasound scan of the urinary tract and an imaging study for VUR. In boys, fluoroscopic micturiting cystourethrogram (MCU) is appropriate to delineate the bladder and urethral anatomy as well as VUR. In girls, MCU or direct radionuclide cystogram (RNC) are appropriate options.

(Level III Evidence, Grade B Recommendation)

DMSA renal scan may help in the following situations: a) A DMSA scan may be needed as soon as possible if the diagnosis of pyelonephritis is strongly suspected but urine culture is not confirmatory. b) A late DMSA scan after 6-12 months can assess permanent renal scarring (as a baseline for monitoring treatment of VUR or as an aid to decide the need for long term follow up).

(Level III Evidence, Grade B Recommendation)

Low dose antibiotic prophylaxis is indicated in the following situations where the risk of recurrent UTI is considered high :

- Grade III-V vesicoureteric reflux ***(Level Ib Evidence; Grade A Recommendation)***
- Recurrent UTI ***(Level Ib Evidence; Grade A Recommendation)***

The optimal duration of prophylaxis is controversial. The need for prophylaxis for Grade I-II vesicoureteric reflux, or for renal scarring without VUR are controversial.

Children with no detected abnormalities on USG, MCU initially, and on DMSA scan at one year follow-up, and having no voiding dysfunction symptoms and no recurrent UTI, may not need further monitoring.

(Level IV Evidence, Grade C Recommendation)

Introduction

This guideline refers to the investigations and initial management following the first proven episode of urinary tract infection (UTI) in children below 2 years of age. Every effort must be made to differentiate contaminated urine culture results from genuine UTI, instead of labeling patients as suspected UTI. When we decide on further investigations, the benefits to individual patient have to be weighed against the psychological stress, discomfort, and economic costs of the investigations. Also parents have to be fully informed and their preference has to be taken into consideration.

In formulating our recommendations, we have adapted heavily from several recent guidelines published by the American Academy of Pediatrics (AAP),[1,2] Royal College of Physicians,[3] the Swedish Medical Research Council[4] and American College of Radiology.[5] This was supplemented by literature search in Medline from 1997 to 2000. It is also important to consider the acceptability by the local profession and community.

Recommendations: 1A. Follow-up investigations are directed to detect underlying anatomical abnormalities of the urinary tract and vesicoureteric reflux (VUR), to assess renal functions and degree of scarring of each kidney, and to look for bladder dysfunction.

1B. Follow-up management are directed to prevent, detect and treat any recurrent UTI, to manage any urological abnormalities appropriately, and hence prevent further renal scarring and its long term sequalae.

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

Notes:

- A meta-analysis by AAP of 77 studies on the prevalence of VUR in children with UTI reported wide variations in prevalence, but as sample size grows, the prevalence converges at 30-40%. When only studies of children below 3 years were pooled, the prevalence was 50%.[1]
- A conventional overview by Dick and Feldman reported that obstructive uropathy are found in 0-4% and VUR in 8-40% of children being investigated for first UTI.[6]
- Bachelard et al. used video-cystometry to study 90 male and 68 female infants with UTI and detected unstable bladder in 2/3 of cases, which was manifested as high voiding pressure and low bladder capacity.[7] Most will resolve with increasing age. However bladder dysfunction should be investigated and treated before considering reflux surgery.
- A review of more than 48 references showed that the rates of renal scarring in children with febrile UTI and VUR were between 1% to 40%. High grade VUR are four to six times more likely to have scarring than those with low grade VUR and 8-10 times as likely as those without VUR.[1]
- Jodal et al. showed that the risk of renal scarring increased exponentially with the number of episodes of UTI.[8]
- Long term studies showed that ESRD develops in 3-10% of patients with extensive scarring.[1]

Recommendations: 2. Clinical assessment should include inquiry into bowel and bladder habits, documenting signs of chronic renal failure, hypertension, palpable kidneys and bladder, lumbosacral spinal abnormalities, weak urine stream (in boys), and serum creatinine level. In children with any abnormalities, the schedule for follow up investigations should be accelerated.

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

Note:

- Based on the recommendation by expert panel.[3,4]

Recommendations: 3. A prophylactic antibiotic should be given to cover the period while waiting for investigations. It can be stopped if significant vesicoureteric reflux and obstructive uropathy are ruled out.

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

Notes:

- Based on the recommendation by expert panels.[3,4]
- The commonly used antibiotics for prophylaxis are trimethoprim (1-2 mg/kg/day), cotrimoxazole (12 mg/kg/day), nitrofurantoin (1 mg/kg/day), nalidixic acid (12.5 mg/kg/day), cefaclor (15-17 mg/kg/day). Generally these doses are 20-30% of the full dosage, given as a single bedtime dose. These antibiotics were preferred because of appropriate activity spectrum, good oral absorption, urine concentration, and their demonstrated efficacy and safety in previous studies.[9]

Recommendations: 4. It is important that the family be educated to recognise the symptoms and signs of recurrent UTI, and be advised to seek immediate medical care when UTI is suspected. It is mandatory to check for UTI recurrence when the diagnosis is suspected. It is optional to test urine microscopy and culture regularly every 3 months.

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

Notes:

- Based on recommendation by expert panel.[4]
- Winberg et al. reported in 1974 their epidemiological study of 596 children after first symptomatic UTI. The recurrence rates were 32% for boys over 1 year old and 40% for girls of all ages. Twenty-nine percent of girls had recurrence in the first year after the index infection.[10]
- The practice of screening urine in asymptomatic patients once every 3 months is declining. Treatment of asymptomatic bacteriuria does not affect the long term prognosis.[11,12] Furthermore, following the use of antibiotics for other infections in the presence of asymptomatic bacteriuria, the child is more prone to be infected with a more virulent organism.[11,13] These observations were made in infants detected to have asymptomatic bacteriuria on population screening, or in older children. Whether they apply to infants with a previous documented UTI is controversial.

Recommendations: 5. It is strongly recommended to do ultrasound scan of the urinary tract and an imaging study for VUR. In boys, fluoroscopic micturiting cystourethrogram (MCU) is appropriate to delineate the bladder and urethral anatomy as well as VUR. In girls, MCU or direct radionuclide cystogram (RNC) are appropriate options.

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

Notes:

- The USG can detect anatomical abnormalities such as dilatation, cysts and ureteroceles. It can also assess renal sizes and symmetry. It can assess bladder wall thickness. USG is comparable to IVU in sensitivity and accuracy in detecting anatomical abnormalities. USG is not as sensitive as DMSA renal scan to detect acute pyelonephritis or renal scars.[5,14] USG as is routinely performed in a service department is not sensitive in detecting VUR. An adequate USG examination consists of assessment of the transverse and longitudinal sections of both kidneys (kidney length or volume; corticomedullary differentiation), any dilatation of the pelvi-calyceal system and the proximal and distal ureters, the anatomy of the bladder (outline of lumen, wall thickness, and efficiency of emptying).
- The MCU is performed to identify any VUR, obstructive anomalies such as posterior urethral valves or ureteroceles. It also provides information on the International Grading of VUR.[5] Infection may affect the result of MCU. Though it is generally recommended to do it at one month after UTI, recent studies showed that a one-week delay is sufficient.[15]
- In a theoretical model of risk analysis and marginal cost-effectiveness analysis, the AAP compared 3 imaging strategies: no evaluation, USG alone, USG plus MCU. They reported that USG alone will prevent almost 3 cases of ESRD or hypertension per 1000 studies done at a cost of US$260,000 per case prevented. An additional MCU prevents an additional one case of ESRD or hypertension per 1000 studies over USG at a cost of US$353,000 per case.[1] No such analysis was available in the local situation.
- Direct radionuclide cystogram (RNC) is an alternative method for detecting VUR. Its advantages are equal or better sensitivity than MCU with lower radiation exposure. Its disadvantage is lack of spatial resolution.[5,16]

Recommendations: 6. DMSA renal scan may help in the following situations :

A) A DMSA scan may be needed as soon as possible if the diagnosis of pyelonephritis is strongly suspected but urine culture is not confirmatory.

B) A late DMSA scan after 6-12 months can assess permanent renal scarring (as a baseline for monitoring treatment of VUR or as an aid to decide the need for long term follow up).

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

Notes:

- DMSA renal cortical scan is more sensitive than intravenous urography (IVU) in identifying acute pyelonephritis (when performed within the first months of UTI) and renal scarring (when performed after 6-12 months).[5]
- It must be pointed out that the long term prognostic significance of cortical defects on DMSA scans are not yet clear because of the short history of availability of this test.

Recommendations: 7. Low dose antibiotic prophylaxis is indicated in the following situations where the risk of recurrence of UTI is considered high :

A) Grade III-V vesicoureteric reflux (Evidence Ib; Recommendation A)

B) Recurrent UTI (Evidence Ib; Recommendation A)

The optimal duration of prophylaxis is controversial. The need for prophylaxis for Grade I-II vesicoureteric reflux, or for renal scarring without VUR are controversial.

Notes:

- A meta-analysis found three small RCT studies on antibiotic prophylaxis in children with normal urinary tracts.[17] They were assessed to have low quality. Two studies reported rate ratios (of UTIs in control/treatment groups) of 24.3 (95% CI 3.2-187.5)[18] and 30.6 (95% CI 4.0-231.8).[12] One study found no difference in UTI rates between control and treatment groups.[19]
- The AAP review in 1999 suggested that prophylaxis is 50% effective whether the rates of reinfection or progression of scarring were compared.[1]
- At least two large randomised controlled trials have been performed that showed no benefit of surgical reimplantation over medical prophylaxis alone.
  - A) The Birmingham Reflux Study Group involved 161 children below 2 years old with UTI and VUR of either grades 2 (contrast reached pelvis but not distended calyces) with scarring or grade 3 (contrast reached pelvis and distended calyces). Fifty percent of patients had scarred kidneys at entry. Overall, there were new scarring in 10 kidneys, and progression in 31 kidneys but they were evenly distributed in the antibiotic prophylaxis or the surgical groups (6% versus 5.2%). There was no significant difference in the rates of breakthrough UTIs.[20]
  - B) The International Reflux Study in Children involved 402 children from Europe and 136 children from USA with Grade III and IV VUR.[21] They found again no difference in the rate of breakthrough UTIs, new scars or scar progression between surgical and medical groups, though the medical group tended to have 2.5 times more of febrile UTIs than surgical group.
- There are no clear definitions of recurrent UTI. In the three RCTs on prophylaxis for UTI, patients were recruited if they have 1 to 3 episodes of UTI in the previous year.
- Since the VUR detected by RNC cannot be graded according to the International Grading System, antibiotic prophylaxis is recommended for any VUR detected.

Recommendations: 8. As an alternative to long term follow up, children with no detected abnormalities on USG, MCU initially, and on DMSA scan at one year follow-up, and having no voiding dysfunction symptoms and no recurrence of UTI, may not need further monitoring.

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

Note:

- Based on expert recommendation.[4]

Limitations of Current Recommendations

Most of the current recommendations are based on expert opinion as there are surprisingly little good quality evidence. The investigatory approach was based on a projected cost-effectiveness analysis. There were no randomised controlled trials that directly showed that children who have routine diagnostic imaging after a first UTI are better off than those who do not.[6] There were also no longitudinal data that link directly the presence of VUR in infants with febrile UTI and normal kidneys to the subsequent development of hypertension or ESRD.[1]

Two systematic reviews have pointed out the weak evidence based on data from three small RCTs supporting the use of antibiotic prophylaxis after UTI,[17,22] and emphasised the need for further studies.

The panel could not find any research data addressing some practical questions raised by our colleagues during the consultation process: For example: 1) whether antibiotic cover should be given for MCU; 2) whether the choice of long term antibiotic prophylaxis should follow the sensitivity pattern of bacteria causing the previous UTI; 3) what are the indications for antibiotic prophylaxis for VUR detected by direct radionuclide cystogram; 4) what are the long term consequence of renal scarring as detected by DMSA scans; 5) whether asymptomatic bacteriuria in infants with history of febrile UTI needs to be treated. These may be good topics for further research.

Lastly, this guideline focused on the initial investigations and follow up management of uncomplicated UTI in children below 2 years of age. The long term management of VUR (especially when to repeat imaging tests, when to stop antibiotic prophylaxis, and when to advise surgical treatment for VUR) is beyond our scope. It should be covered by a future exercise, with more collaboration between the paediatric urologists, radiologists and nephrologists.

Acknowledgement

We would like to thank Dr HW Liu and his colleagues of the Clinical Effectiveness Unit of Hospital Authority for their advice in preparing this guideline.

References

1. Downs SM. Technical report: urinary tract infections in febrile infants and young children. The Urinary Tract Subcommittee of the American Academy of Pediatrics Committee on Quality Improvement. Pediatrics 1999;103:e54.
2. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics Committee on Quality Improvement Subcommittee on Urinary Tract Infection. Pediatrics 1999;103(4 Pt 2):843-52.
3. Guidelines for the management of acute urinary tract infection in childhood. Report of a Working Group of the Research Unit, Royal College of Physicians. J R Coll Physicians Lond 1991; 25:36-42.
4. Jodal U, Lindberg U. Guidelines for management of children with urinary tract infection and vesico-ureteric reflux. Recommendations from a Swedish state-of-the-art conference. Swedish Medical Research Council. Acta Paediatr 1999;88: 87-9.
5. Expert Panel on Pediatric Imaging. ACR Appropriateness Criteria: Urinary Tract Infection. 1999; American College of Radiology. 847 p.
6. Dick PT, Feldman W. Routine diagnostic imaging for childhood urinary tract infections: a systematic overview. J Pediatr 1996; 128:15-22.
7. Bachelard M, Sillen U, Hansson S, Hermansson G, Jodal U, Jacobsson B. Urodynamic pattern in infants with urinary tract infection. J Urol 1998;160:522-6.
8. Jodal U. The natural history of bacteriuria in childhood. Infect Dis Clin North Am 1987;1:713-29.
9. Mangiarotti P, Pizzini C, Fanos V. Antibiotic prophylaxis in children with relapsing urinary tract infections: review. J Chemother 2000;12:115-23.
10. Winberg J, Andersen HJ, Bergstrom T, Jacobsson B, Larson H, Lincoln K. Epidemiology of symptomatic urinary tract infection in childhood. Acta Paediatr Scand Suppl 1974;252:1-20.
11. Wettergren B, Hellstrom M, Stokland E, Jodal U. Six year follow up of infants with bacteriuria on screening. BMJ 1990;301: 845-8.
12. Lohr JA, Nunley DH, Howards SS, Ford RF. Prevention of recurrent urinary tract infections in girls. Pediatrics 1977;59: 562-5.
13. Hansson S, Jodal U, Noren L, Bjure J. Untreated bacteriuria in asymptomatic girls with renal scarring. Pediatrics 1989;84: 964-8.
14. Lavocat MP, Granjon D, Allard D, Gay C, Freycon MT, Dubois F. Imaging of pyelonephritis. Pediatr Radiol 1997;27:159-65.
15. Craig JC, Knight JF, Sureshkumar P, Lam A, Onikul E, Roy LP. Vesicoureteric reflux and the timing of micturating cystourethrography after urinary tract infection. Arch Dis Child 1997;76:275-7.
16. Polito C, Rambaldi PF, La Manna A, Mansi L, Di Toro R. Enhanced detection of vesicoureteric reflux with isotopic cystography. Pediatr Nephrol 2000;14:827-830.
17. Le Saux N, Pham B, Moher D. Evaluating the benefits of antimicrobial prophylaxis to prevent urinary tract infections in children: a systematic review. CMAJ 2000;163:523-9.
18. Smellie JM, Katz G, Gruneberg RN. Controlled trial of

prophylactic treatment in childhood urinary-tract infection. Lancet 1978;2:175-8.
19. Lettgen B. Prevention of recurrent urinary tract infections in female children. Curr Ther Res 1996;57:464-75.
20. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children: five years' observation. Birmingham Reflux Study Group. BMJ 1987;295:237-41.
21. Smellie JM, Tamminen-Mobius T, Olbing H, et al. Five-year study of medical or surgical treatment in children with severe reflux: radiological renal findings. The International Reflux Study in Children. Pediatr Nephrol 1992;6:223-30.
22. Williams G, Lee A, Craig J. Antibiotics for the prevention of urinary tract infection in children: A systematic review of randomized controlled trials. J Pediatr 2001;138:868-74.