J Antimicrob Chemother 2010; **65**: 836–841
doi:10.1093/jac/dkq045 Advance publication 4 March 2010

Journal of Antimicrobial Chemotherapy

Microbiological aspects of the UK National Institute for Health and Clinical Excellence (NICE) guidance on urinary tract infection in children

E. Price[1]*, A. Pallett[2], R. D. Gilbert[3] and C. Williams[4]

[1]*Department of Medical Microbiology, Barts and The London NHS Trust, Pathology and Pharmacy Building, 80 Newark Street, London E1 2ES, UK;* [2]*Department of Medical Microbiology, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK;* [3]*Department of Child Health, Southampton General Hospital & University of Southampton, Tremona Road, Southampton SO16 6YD, UK;* [4]*Department of Medical Microbiology, Royal Hospital for Sick Children, Dainair Street, Glasgow G3 8SJ, UK*

*Corresponding author. E-mail: elizabethshanson@btinternet.com

The publication in August 2007 of the UK National Institute for Health and Clinical Excellence (NICE) guidance on urinary tract infection in children provided a fresh and useful review of the management of this condition. However, it has also resulted in some controversy. In particular, the advice to use urgent microscopy for rapid screening of urine in children ≥3 months but <3 years of age has presented practical problems for some laboratories in staffing this service out of hours. Further discussion between microbiologists, paediatricians and primary care doctors regarding this recommendation is required. In addition, the abandoning of routine antibiotic prophylaxis following a first-time urine infection has caused some debate. The evidence around these issues is reviewed, as well as the differences in the laboratory processing and interpretation of paediatric urines compared with urine specimens from adults. General measures to reduce the risk of recurrence are also discussed. As mentioned in the NICE guidance, microbiologists should continue to emphasize the basic principles, particularly the importance of obtaining an accurate diagnosis from a well-collected and well-transported urine specimen.

Keywords: NICE guidance, paediatric urinary tract infection, microscopy, dipsticks, antibiotic prophylaxis

Introduction

The aim of the UK National Institute for Health and Clinical Excellence (NICE) guidance on paediatric urinary tract infection (UTI) is to promote more consistent clinical practice by ensuring prompt, accurate diagnosis and appropriate management of UTI in this important age group. A key feature of the guidance is that infants and children with unexplained fever of ≥38°C should have their urine tested after 24 h at the latest.[1–3] However, as well as providing a useful review of this subject, the guidance has caused some controversy among microbiologists with regard to the best screening test for initial management of possible urine infections in children ≥3 months but <3 years of age. In addition, there has been some uncertainty about the decision to abandon the time-honoured recommendation for routine antibiotic prophylaxis following a first urine infection. These and other issues are discussed below.

Urine screening tests and age of the child

For decisions on urine testing strategies, the NICE guidance has divided children into three groups: those <3 months; those ≥3 months but <3 years; and those ≥3 years of age. The reasons for division at this age are that acceptable urine samples are more easily obtained from the older age group, their symptoms tend to be more specific and they are more able to verbalize them. In contrast, uncontaminated specimens are less easily obtained from the two younger age groups. These children are more likely to have non-specific symptoms, such as malaise, irritability, poor feeding, jaundice, failure to thrive and vomiting. Many will not be toilet trained and this increases the difficulty of obtaining satisfactory samples. However, it may still be worth noting that it is children <2 years (rather than <3 years) who are more likely to have factors predisposing them to renal damage and for whom the possibility of genitourinary tract abnormalities associated with UTI is greater.[4]

In assessing the recommendations in the NICE guidance for urine screening tests, microbiologists and paediatricians need to be aware that there is no rapid screening test that will detect all paediatric UTIs. The two main screening methods in use are dipstick testing and conventional microscopy, but false-positive and false-negative results may occur with both of them. For dipsticks, the NICE guidance found that performance was generally less diagnostic in infants and younger children than in the older paediatric age groups. The reasons for this

age difference may relate in part to the small capacity and frequent emptying of the infant bladder, resulting in lower numbers of organisms and less pyuria. Also, different collection methods for infants and contamination of samples may be relevant factors. With regard to microscopy, the NICE guidance reported difficulty in drawing conclusions about diagnostic accuracy because of lack of data and heterogeneity between studies. It was also noted that a certain amount of expertise was necessary for undertaking microscopy.

Children <3 months

The NICE guidance recommends that infants <3 months of age should have urgent urine microscopy carried out. These infants are likely to have other specimens as well as urines sent and all of these will need urgent culture. Such infants, as well as older children with a high risk of serious illness, should be referred for paediatric specialist care and managed in line with 'Feverish illness in children' from the NICE clinical guideline 47.[5]

Children ≥3 months but <3 years

For children ≥3 months but <3 years with non-specific symptoms and a high risk of serious illness, the NICE guidance recommends urine microscopy and advises that it should be carried out urgently. This is also the approach preferred by the NICE guidance for children in this age group with either an intermediate risk of serious illness or with specific urinary symptoms, although it is noted that under these circumstances this test may not always be available urgently. (Particularly in primary care, if urgent microscopy is not available, the NICE guidance takes the pragmatic view and accepts that dipsticks may be used for children ≥3 months but <3 years who have non-specific symptoms but are relatively well.)

In the comparison of microscopy and dipsticks, the NICE guidance looked at studies that examined results stratified by age. They found only one study that satisfied their criteria and divided children into separate groups near to 3 years of age. This was a 1991 American study that considered children under and over 2 years of age,[6] and it was the only study included in this part of the analysis. The urine samples were obtained by a variety of methods, including urine bags, clean catch specimens and diagnostic urethral catheters. Results from urine microscopy using a centrifuged deposit and a cut-off of either 5 or 10 white blood cells per high power field (WBCs/hpf) were compared with dipstick results where both nitrite *and* leucocyte esterase (LE) tests were positive. Some of the results were then used by NICE to calculate likelihood ratios for ruling in and ruling out the diagnosis of UTI.

For ruling in the diagnosis of UTI in children <2 years from the above study, NICE found that microscopy with a 10 WBCs/hpf cut-off performed better than dipsticks. (When 5 WBCs/hpf was the cut-off, neither test did well, but dipsticks had the better performance.) For ruling out the diagnosis of UTI in children <2 years, microscopy with a cut-off of 5 WBCs/hpf performed better than dipsticks, but the difference was marginal. However, it should be noted that the 95% confidence intervals overlapped, both for ruling in and ruling out the diagnosis, so these findings may or may not be significant.

A further factor to note is that the microscopy method employed in the above study considered by the NICE guidance is probably no longer used by many UK microbiology laboratories. Centrifuging urines can be laborious and time consuming for laboratory staff, and microscopy on uncentrifuged specimens may be used instead. Automated methods are also in use in many departments, although these methods have been primarily validated for adult urines.

More recent reports on urine screening methods from the same American group have investigated larger numbers of children <2 years[7,8] and the urine specimens were mainly obtained by urethral catheter. These reports were not included in the NICE guidance, possibly because slightly different criteria and definitions were used. In one study, dipsticks were found to be slightly more sensitive and specific than microscopy for this age group.[7] In the other study, the authors concluded that treatment should be started following a positive dipstick result (at least a moderately strongly positive LE test or a positive nitrite test).[8] Combinations of screening tests including Gram stain were also investigated.[4,8] In one of these studies in children <2 years, microscopy plus Gram stain was the most sensitive test, but it was slightly less specific than the other tests and more expensive. The authors suggested that it should be reserved for neonates or subsets of children at particularly high risk for UTI.[8]

Action required: the urine screening recommendations from the NICE guidance for children ≥3 months but <3 years need further discussion between microbiologists, paediatricians and primary care doctors

The NICE guidance recommendation for urine microscopy to be carried out urgently in certain children ≥3 months but <3 years specified above, has implications for microbiology laboratory resources. Discussions between microbiologists and paediatricians are needed,[2] especially in view of the limitations of the data on which this recommendation is based, as mentioned above. Many microbiology laboratories will only be able to provide urgent urine microscopies up to 23.00 h or midnight. After this time it would be more difficult to staff the service, particularly if no other specimen requiring immediate processing (such as a CSF) has been sent from the same patient. It may be argued that a sick child will be given antibiotics anyway once a satisfactory urine specimen has been collected. After being tested by the dipstick method, the specimen could be refrigerated and microscopy carried out first thing in the morning. (There will be no advantage in carrying out urgent urine culture after midnight, as cultures are unlikely to be readable during the next working day.) It may also be worth noting that the full version of the NICE guidance states that a child in this age group with non-specific symptoms and a low risk of serious illness can be observed without giving antibiotics until the results of standard (not urgent) microscopy are available. This can be especially useful if the diagnosis is in doubt and it will allow time for a second urine to be collected.

Children ≥3 years

For children ≥3 years old with a possible first time lower UTI, the NICE guidance recommends dipstick testing. For ruling in the

diagnosis using the same 1991 American study,[6] dipsticks performed better than microscopy at the 5 WBCs/hpf cut-off and the 95% confidence intervals did not overlap. NICE therefore concluded that dipsticks with positive nitrite *and* LE tests were better than microscopy for ruling in the diagnosis of UTI in this older age group. (At the 10 WBCs/hpf cut-off, although dipsticks had a higher likelihood ratio than microscopy for ruling in the diagnosis, the 95% confidence intervals overlapped, so the result at this higher WBC cut-off may or may not be statistically significant.) For ruling out the diagnosis of UTI, the NICE guidance found no statistically significant difference between microscopy and dipsticks.

A useful table is given by the NICE guidance for management following different combinations of LE and nitrite results. As for adults, false-positive nitrite tests are uncommon. The specificity of this test is high, although the sensitivity is relatively low. Presence of nitrites suggests infection if a fresh, well-collected urine has been tested, and in these circumstances the NICE guidance recommends giving antibiotics and sending a urine culture. The presence of WBCs, as indicated by a positive LE test, is common in UTIs but may also occur in other conditions. Particularly in children, WBCs can be present for many reasons, including fever alone.[9]

New NICE recommendations for urine culture

For children <3 years, the NICE guidance recommends that all urines should be cultured. For children ≥3 years of age, it is considered that a urine with a negative LE and nitrite test does not need to be cultured unless the patient has a high to intermediate risk of serious illness, has recurrent UTI or is in one of the other indication groups for culture listed in the guidance (including an infection that does not respond to treatment within 24–48 h). All urines with a positive test for either nitrite or LE should be cultured. It will be necessary for both microbiologists and paediatricians to maintain high awareness of the age of the child whose sample is being tested.

Discontinuation of routine antibiotic prophylaxis

A major change in the NICE guidance is that routine antibiotic prophylaxis following a first-time UTI is no longer recommended, although it may be considered for certain infants and children with recurrent UTI. The evidence examined included a meta-analysis of results from randomized controlled trials, and particular attention was given to children with asymptomatic bacteriuria and to children with vesicoureteric reflux (VUR). Although limited by the heterogeneity of the trials, the NICE guidance was able to conclude that prophylactic antibiotics reduced bacteriuria, but there was no high-level evidence that they were effective in preventing further symptomatic UTIs and renal scarring, the most important outcomes for the patient. This conclusion has subsequently been supported by a further publication.[10] No controlled studies have shown that prophylaxis is better than prompt treatment of UTI for the prevention of renal scarring.[11]

In addition, mild/moderate VUR has not been reported to increase the incidence of UTI, pyelonephritis or subsequent renal scarring.[12] It is of interest that the NICE guidance has recommended a reduction in some routine imaging following UTI.

The increased risk of development of resistant organisms following prophylactic antibiotics was also considered in the NICE guidance. Such an increase has been shown in recent studies from the USA, Australia and Italy.[13–16] This should not be surprising, as prophylactic antibiotics have been given at low dose and may continue over fairly long periods of time. When antibiotic prophylaxis was first recommended, co-trimoxazole was a common initial choice. However, following concerns about potential adverse effects from the sulphonamide component, trimethoprim alone was commonly used in the UK for treatment and prophylaxis, although co-trimoxazole remains in frequent use for urinary prophylaxis in other countries.

Resistance to trimethoprim in paediatric UTIs has also been increasing in the UK.[11,17,18] As for adults, it can be queried whether the incidence of trimethoprim resistance in hospital is an accurate reflection of community resistance.[19] However, in 2006, the Welsh Antimicrobial Resistance Programme found an incidence of 27.3% and 26.5% for trimethoprim resistance in hospital and community specimens, respectively, in children <6 years old [R. Howe, Microbiology Cardiff (Velindre NHS Trust), University Hospital of Wales, Cardiff, UK, personal communication]. Other hospital-based figures for children can be higher than this, as hospital units see more patients with complicated or recurrent infections.[17,18]

An increased risk of trimethoprim resistance has been shown in the 3 months following taking trimethoprim[20] and such an increase is likely to include trimethoprim taken as prophylaxis. In one study, 28% of children with community-acquired trimethoprim-resistant UTIs had been given trimethoprim previously, usually for treatment and prophylaxis of a trimethoprim-susceptible urine infection.[18] Other factors that may be relevant for trimethoprim-resistant UTIs include exposure to other antibiotics,[21] intrafamilial spread of organisms[22] and travel.[23] When trimethoprim was given as an initial treatment for a trimethoprim-resistant urinary infection, most patients were still symptomatic at 48 h.[18]

Although β-lactam antibiotics were not recommended for prophylaxis in the 1991 Royal College of Physicians (RCP) Guidelines on UTI in childhood,[24] they have crept into use for this purpose, especially cefalexin.[17,25–27] An increase in resistant organisms is predictable with this group of antibiotics, as well as overgrowth of opportunist organisms, such as *Candida* and *Pseudomonas* spp., and selection for methicillin-resistant *Staphylococcus aureus*. In addition, cefalexin may select for extended-spectrum β-lactamase-producing Gram-negative bacteria, which can be causes of UTI.[15,28]

Nitrofurantoin has also been used for prophylaxis, but this agent is not well tolerated by some children.[11] It is contraindicated in children <3 months of age and can be neurotoxic in patients with reduced renal function. Nitrofurantoin has a significant number of other side effects and is ineffective against *Proteus* spp.

Further problems relating to the use of prophylactic antibiotics for paediatric UTIs are that they are inconvenient for the patient and compliance is not always good. In addition, the cost of the drugs has to be taken into account as well as the risks that can be associated with any medication.[10]

General measures to reduce recurrence of UTI

Many of the general measures aimed at reducing the risk of recurrence of infection (particularly in girls) that were listed in the Appendix of the 1991 RCP paediatric UTI guidelines[24] have not been included in the NICE guidance. Although evidence may be limited for some of the recommendations, most of them are common-sense measures. They include advice on regular bladder emptying, cleaning the perineal/anal area from front to back after toilet, treating constipation adequately, and avoiding both bubble baths and washing the hair in the bath. Parents of children with a previous UTI may find such lists helpful.

The need to encourage children who have had a UTI to drink an adequate amount of fluids each day was mentioned in the NICE guidance, although this recommendation could be given more prominence. The protective effect of breastfeeding against UTI was also mentioned. The guidance noted that uncircumcised boys are at slightly higher risk of UTI than circumcised boys and in boys with abnormal urinary tracts, circumcision may be indicated to prevent recurrent UTI.

Collection of urine specimens from children

Although we agree with the NICE guidance when it mentions the need for well-collected and rapidly transported urines, these requirements could always benefit from further emphasis. If collection of a urine specimen is carried out badly, the future management of the child may be compromised. This could mean delayed treatment for a child with a genuine UTI, if a badly taken specimen is mistakenly considered to show contamination only. Conversely, it could result in the giving of unnecessary antibiotics or the instigation of unnecessary imaging investigations if a contaminated sample is mistakenly considered to indicate the presence of a UTI. At least one well-collected, uncontaminated sample should be taken before antibiotics are started.

The NICE guidance commented that a clean catch urine specimen was the least contaminated non-invasive sample and it was their recommended method for urine collection. In our experience, these specimens are not really that difficult to collect, even from little girls. However, one study reported that many parents disliked clean catch specimens, as they found them messy and time consuming.[29] Even so, it could be useful if staff and parents were informed about the importance of collecting this recommended specimen, as it is the best of the non-invasive methods and decisions regarding the child's future treatment will be based on its results. They could be told that patience and the acceptance of the occasional accident or wet floor might be necessary. The guidance noted that urine bags were distressing, uncomfortable and had a high contamination rate. Urine collection pads were more comfortable and cheaper than urine bags. They were considered to be a non-invasive option if a clean catch urine sample was not possible and in the study mentioned previously,[29] urine pads were the method preferred by many parents. However, contamination rates for bags and pads have been reported to be similar.[30] One study suggested that accuracy of urine collection pads was improved if they were not used for >30 min.[31] NICE added that sanitary towels, gauze, cotton wool balls and panty liners placed in the nappy may contain bactericidal materials, and are therefore unsuitable for urine collection.

If the above methods are not possible or are unsuccessful, in/out urethral catheter or ultrasound-guided suprapubic aspirates are recommended.

The NICE guidance considers that parents and carers should be involved in making decisions about their child's care. As mentioned above, it could be useful if some parents or carers were involved in the actual collection of the sample, especially during any subsequent febrile episode for a child who has already had a UTI. Also, if specimen collection is difficult in primary care, easy access to an outpatient paediatric unit would be useful, so that an acceptable specimen could be collected by expert staff.

As mentioned by the guidance, once a satisfactory sample has been collected, it should reach the laboratory within 4 h of voiding.

Interpretation of culture results from paediatric urine specimens

The NICE guidance emphasizes that results from urine culture should be interpreted in relation to the clinical symptoms and findings. It mentions the cut-off value of 10^5 cfu per mL of a single organism as being the usually accepted laboratory indicator of UTI, but it also recognizes that lower amounts of growth, as well as the very occasional mixed culture, may be significant in some children. Especially in small male infants, the urine may not always remain in the bladder long enough to reach 10^5 cfu per mL—a figure originally worked out in adult women and not formally validated in children. If there is uncertainty regarding the significance of a culture result, a second urine taken before antibiotics are started can be helpful, as long as the delay is clinically acceptable.

There are a few further paediatric issues that microbiology laboratories should be aware of that are not discussed in detail in the NICE guidance. In paediatric practice, the level at which a growth is considered significant can vary according to the collection method used.[7,13,32] With the provisos mentioned above, usually $\geq 10^5$ cfu per mL of a single organism is considered significant for clean-catch urines. For in/out catheter urines this figure is $\geq 10^4$ cfu per mL[7,13,26] and for supra-pubic aspirates any growth should be reported, as this specimen should be sterile if taken correctly in the absence of a UTI. In addition, it is important for laboratories to be aware that diagnostic in/out catheter specimens from children need to be processed and interpreted differently from in-dwelling urinary catheter specimens. Clinicians need to ensure clear information is given when submitting specimens. Laboratories should also know that two urines taken over a few hours from a child should both be accepted for processing rather than one being discarded, as happens occasionally.

Communication of the results

This area was not considered by the NICE guidance. However, the problem of poor communication of results deserves further consideration, especially as there could be legal implications if appropriate action is not taken.[33]

Future research

Among the recommendations for further research, NICE mentions a cohort study of the long-term outcomes of paediatric UTIs in the UK and further investigation into the use of dipsticks in the different paediatric age groups. In addition, an audit of the availability (or otherwise) of urgent microscopy after 23.00 h in UK microbiology laboratories would be of interest.

Costing the changes recommended by NICE

A separate costing report has been produced to accompany the NICE guidance.[34] There will certainly be some extra costs from an increase in out-of-hours urines from children ≥3 months but <3 years of age. This is of relevance for microbiology departments and will need to be reviewed. However, issues related to cost will vary a great deal depending on the out-of-hours working pattern employed by individual hospitals. For example, if a laboratory undertakes shift work, the costs will be much less than in a laboratory where each call is costed separately. Local population factors and local circumstances will also be relevant in assessing the financial impact of the changes. Costs may be offset to some extent by a decrease in the number of urines needing culture from children ≥3 years of age. There will also be financial savings from the discontinuation of routine antibiotic prophylaxis and reduced routine imaging, as well as from a saving in clinician time.

Conclusions

Although some aspects of the NICE guidance are controversial,[35–37] it provides a fresh and useful review of the management of paediatric UTI. Attention is given to avoiding over or under diagnosis or investigation and to the prompt start of appropriate treatment. Microbiologists can play a valuable role by continuing to emphasize the basic issues, especially the importance of obtaining a quick and accurate diagnosis from a well-collected and well-transported urine specimen.

Transparency declarations

C. W. was a member of the NICE urinary tract infection in children guideline development group. All other authors: none to declare

References

1 National Collaborating Centre for Women's and Children's Health. *National Institute for Health and Clinical Excellence (NICE) Guideline. Urinary Tract Infection in Children: Diagnosis, Treatment and Long-term Management*. London: RCOG Press, 2007. http://www.nice.org.uk/nicemedia/pdf/CG54fullguideline.pdf (10 February 2010, date last accessed).

2 Baumer JH, Jones RWA. Urinary tract infection in children, National Institute for Health and Clinical Excellence. *Arch Dis Child Educ Pract Ed* 2007; **92**: 189–92.

3 Mori R, Lakhanpaul M, Verrier-Jones K. Diagnosis and management of urinary tract infection in children: summary of NICE guidance. *BMJ* 2007; **335**: 395–7.

4 Zorc JJ, Kiddoo DA, Shaw KN. Diagnosis and management of pediatric urinary tract infections. *Clin Microbiol Rev* 2005; **18**: 417–22.

5 National Collaborating Centre for Women's and Children's Health. *National Institute for Health and Clinical Excellence (NICE) Guideline. Feverish Illness in Children: Assessment and Initial Management in Children Younger Than 5 Years*. London: RCOG Press, 2007. http://www.nice.org.uk/nicemedia/pdf/CG47Guidance.pdf (10 February 2010, date last accessed).

6 Shaw KN, Hexter D, McGowan KL *et al*. Clinical evaluation of a rapid screen test for urinary tract infections in children. *J Pediatr* 1991; **118**: 733–6.

7 Shaw KN, McGowan KL. Evaluation of a rapid screening filter test for urinary tract infection in children. *Pediatr Infect Dis J* 1997; **16**: 283–7.

8 Shaw KN, McGowan KL, Gorelick MH *et al*. Screening for urinary tract infection in infants in the emergency department: which test is best? *Pediatrics* 1998; **101**: E1.

9 Turner GM, Coulthard MG. Fever can cause pyuria in children *BMJ* 1995; **311**: 924.

10 Mori R, Fitzgerald A, Williams C *et al*. Antibiotic prophylaxis for children at risk of developing a urinary tract infection: a systematic review. *Acta Pediatr* 2009; **98**: 1781–6.

11 Verrier Jones K. Prognosis for vesicoureteric reflux. *Arch Dis Child* 1999; **81**: 287–9.

12 Garin EH, Olavarria F, Nieto VG *et al*. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. *Pediatrics* 2006; **117**: 626–32.

13 Lutter SA, Currie ML, Mitz LB *et al*. Antibiotic resistance patterns in children hospitalized for urinary tract infections. *Arch Pediatr Adolesc Med* 2005; **159**: 924–8.

14 Conway PH, Cnaan A, Zaoutis T *et al*. Recurrent urinary tract infections in children: risk factors and association with prophylactic antimicrobials. *JAMA* 2007; **298**: 179–85.

15 Craig JC, Simpson JM, Williams GJ *et al*. Antibiotic prophylaxis and recurrent UTI in children. *New Engl J Med* 2009; **361**: 1748–59.

16 Montini G, Rigon L, Zucchetta P *et al*. Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. *Pediatrics* 2008; **122**: 1064–71.

17 Ladhani S, Gransden W. Increasing antibiotic resistance among urinary tract isolates. *Arch Dis Child* 2003; **88**: 444–5.

18 Hajibagheri K, Priesemann M, Morrison I *et al*. NICE guidance on urinary tract infection in children abandons routine antibiotic prophylaxis. *Arch Dis Child* 2008; **93**: 356.

19 McNulty CAM, Richards J, Livermore DM *et al*. Clinical relevance of laboratory-reported antibiotic resistance in acute uncomplicated urinary tract infection in primary care. *J Antimicrob Chemother* 2006; **58**: 1000–8.

20 Hillier S, Roberts Z, Dunstan F *et al*. Prior antibiotics and risk of antibiotic-resistant community-acquired urinary tract infections: a case-control study. *J Antimicrob Chemother* 2007; **60**: 92–9.

21 Magee JT, Pritchard EL, Fitzgerald KA *et al*. Antibiotic prescribing and antibiotic resistance in community practice: retrospective study, 1996–8. *BMJ* 1999; **319**: 1239–40.

22 Rydberg J, Cederberg A. Intrafamilial spreading of *Escherichia coli* resistant to trimethoprim. *Scand J Infect Dis* 1986; **18**: 457–60.

23 Murray BE, Mathewson JJ, DuPont HL *et al*. Emergence of resistant fecal *Escherichia coli* in travelers not taking prophylactic antimicrobial agents. *Antimicrob Agents Chemother* 1990; **34**: 515–8.

24 Anon. 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.

25 *British National Formulary for Children 2009*. Cefalexin (Cephalexin). Prophylaxis of recurrent urinary-tract infection. Section 5.1.2.1. BMJ Group, RPS Publishing, RCPCH Publications Ltd, 2009.

26 Hoberman A, Wald E. Urinary tract infections in young febrile children. *Pediatr Infect Dis J* 1997; **16**: 11–7.

27 Cheng CH, Tsai MH, Huang YC *et al*. Antibiotic resistance patterns of community-acquired urinary tract infections in children with vesicoureteral reflux receiving prophylactic antibiotic therapy. *Pediatrics* 2008; **122**: 1212–7.

28 Calbo E, Romaní V, Xercavins M *et al*. Risk factors for community-onset urinary tract infections due to *Escherichia coli* harbouring extended-spectrum β-lactamases. *J Antimicrob Chemother* 2006; **57**: 780–3.

29 Liaw LCT, Nayar DM, Pedlar SJ *et al*. Home collection of urine for culture from infants by three methods: survey of parents' preferences and bacterial contamination rates. *BMJ* 2000; **320**: 1312–3.

30 Macfarlane PI, Houghton C, Hughes C. Pad urine collection for early childhood urinary-tract infection. *Lancet* 1999; **354**: 571.

31 Rao S, Bhatt J, Houghton C *et al*. An improved urine collection pad method: a randomized clinical trial. *Arch Dis Child* 2004: **89**: 773–5.

32 Williams G, Craig JC. Diagnosis and management of urinary tract infections (Chapter 35). In: Geary DF, Schaefer F, eds. *Comprehensive Pediatric Nephrology*. Philadelphia: Mosby Elsevier, 2008; 539–48.

33 Medical Protection Society. Missed test result. *United Kingdom Casebook* 2008; **16**: 19.

34 National Institute for Health and Clinical Excellence. *Urinary Tract Infection in Children. Costing Report and Costing Template*. London: NICE, 2007. http://guidance.nice.org.uk/CG54 (10 February 2010, date last accessed).

35 Watson AR. Management of urinary tract infection in children. *BMJ* 2007; **335**: 356–7.

36 Coulthard MG. NICE on childhood UTI: nasty processes produce nasty guidelines. *BMJ* 2007; **335**: 463.

37 Watson AR. Author's reply. *BMJ* 2007; **335**: 463–4.