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EDITORIAL COMMENTARY

Difficulties in diagnosing urinary tract infections in small children

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Abstract Urinary tract infections (UTIs) in children appear to be simple and straightforward matters, but there is as yet no consensus on UTIs in this patient group, and it remains one of the most – if not the most – controversial fields in paediatric medicine. Controversy and the lack of consensus can be found in many areas, including the diagnosis and management of UTIs in paediatric patients. Consequently, children with a UTI are investigated and treated quite differently in different parts of the world and also within different parts of the same country. One factor contributing to the current situation is the unexpected difficulty in diagnosing a UTI in children. This difficulty has implications not only for clinical work but also for scientific studies. Substantial over- and under-diagnosing can result from practical difficulties in at least three areas, including problems with collecting urine samples, in interpreting bacterial numbers correctly, and in confusing infantile asymptomatic bacteriuria and a true symptomatic febrile UTI. In this review, these problems will be discussed in detail as well as the implications they have had on clinical practice and research on UTIs.

Keywords urine tract infection · bacterial numbers · contamination · asymptomatic bacteriuria

Introduction

On the face of it, urinary tract infections (UTI) in children seem to be a simple and straightforward matter, and yet the treatment of UTI is one of the most—if not the most—controversial areas of paediatric medicine. As an example, the recent UK guidelines from NICE (National Institute of Health and Clinical Excellence) were greeted in very different ways. In the UK itself, one response was "Nasty processes produce Nasty guidelines" [1], while in Sweden, the response was "English guidelines—nothing for children with urinary tract infections in Sweden" [2]. A recent report from Australia did, however, give a very different opinion "in Australia at least, it may be a case of guidelines catching up with changes in clinical practice rather than the other way" [3].

These controversies are reflected in many ways, one of which is the large variation in the number and types of follow-up investigations children receive after a UTI. A comparison between 25 children's hospital in the USA showed that between a few percent up to 75% of children had an micturating cystourethrogram (MCUG) after their UTI [4]. Similarly, in a survey of 23 different American hospitals, the "typical" patient, a 6-year-old girl with private insurance and low disease severity, had a very variable chance to be treated with endoscopic injection, namely, between 7 and 85% depending on the choice of hospital [5].

How can this be? Children with UTI are very common, and there has been plenty of opportunity to study them and to come to conclusions upon which most paediatricians could agree. However, such a consensus has not seemed to have been reached. The most important disagreements surround the care of younger children with UTI. Here, I discuss a number of important issues regarding the diagnosis of a UTI, with a specific focus on bacteriuria, which I suggest should be given more attention when future studies are being designed.

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Bacterial cultures

Bacterial numbers of 10^5 colony-forming units (CFU)/ml or more are normally regarded as significant growth. This cut-off point dates back to a few papers by Ed Kass in the 1950s who defined a level of bacterial count that would include most patients with true UTI without including too many without a true infection. In his initial publication, however, he acknowledged that the proposed cut-off would lead to a number of false negative diagnoses [6].

Anecdotal data from case series have suggested that a proportion of children with true infections have urine cultures with fewer than 10^5 bacteria [7]. A large population-based study from Sweden found that 73 (20%) of 366 infants with a symptomatic UTI had colony counts of $<10^5$ CFU/ml [8] based on cultured urine specimens obtained by suprapubic aspiration (SPA). A Finnish study in 477 infants found bacteria in urine specimens collected by SPA in 322 infants, and of these only 81% showed $>10^5$ CFU/ml in a clean voided urine specimen [9]. Bacterial numbers in the 19% of children who would have been missed on the basis of the clean voided specimen ranged from 10^4 (18 children) to 10^3 (20 children) CFU/ml.

It is well established that different cut-off levels are used for bag cultures, SPAs and cultures from catherised samples. This is not very logical in the biological sense as there is no scientific evidence demonstrating that bacteria will have grown exponentially during their transport through the urethra. The different cut-off levels have been decided upon based on the risk of contamination of the bag cultures.

A recent study that used different cut-off levels for bag samples ($\geq 10^6$) and catheter samples ($\geq 10^3$) found that there were 29% false negative bag cultures compared to the catheter samples [10]. Children with true infections can thus be missed both in clinical practice and in scientific studies.

Contaminated cultures

Contaminated cultures can be quite a substantial problem—particularly in small children. This was emphasised as early as in studies carried out in the 1970s. A study involving 120 infants and children showed a 25% contamination rate with samples from clear-voided urine compared to samples from suprapubic aspiration [11]. Investigators from the Royal Free Hospital in London also emphasised that a true single organism growth could be hidden in mixed growth from a bag or clean catch sample [12]. A number of subsequent studies have reported quite varying contamination rates. Al Orifi et al. reported 62.8% false positive cultures [13], while a recent study reported a 7.5% contamination rate [10].

This high risk for contaminated cultures is very easy to understand when you know how small children pass urine. Small boys do regularly flush their prepuce and small girls do regularly flush their vagina (Figs. 1, 2). Consequently, it is very difficult to collect a clean urine sample outside of the body of small children.

Asymptomatic bacteriuria

Asymptomatic bacteriuria (ABU) is quite a common, but not always well recognised, and therefore represents a further complication to making the correct diagnosis of a symptomatic UTI. This is particularly true in infants. Few studies have systematically examined this aspect of pediatric nephrology, but one very well performed Swedish study from 1990 cultured specimens from all 3581 infants born during 1 year in one specific catchment area of Gothenburg. All infants had bag urine cultures performed at 2 weeks, 3 months and 10 months of age. Positive cultures were always confirmed with a culture of urine collected by a supra-pubic bladder puncture [14].

A minimum of 2.5% of the boys and 0.9% of the girls showed signs of ABU during their first year of life (Figs. 3, 4). In the same cohort of children, another 1.2% of the boys and 1.1% of the girls developed an episode of febrile symptomatic UTI. Follow-up studies showed that the ABU lasted between 0.5 and 7.5 months (median of 2 and 1.5 months for the girls and boys, respectively) and had resolved spontaneously without any signs of kidney scarring by the 6-year follow-up [14–16]. A subsequent Turkish study which only used clean catch cultures, without confirmation on urine collected by SPA, showed a prevalence of bacteriuria in 4% of newborns and 5.2% of infants [17].

Consequences of the difficult diagnosis of febrile UTI

An infant with ABU (in nearly all cases not previously diagnosed) will pose a major diagnostic challenge when he/she develops fever from a normal viral disease. It will

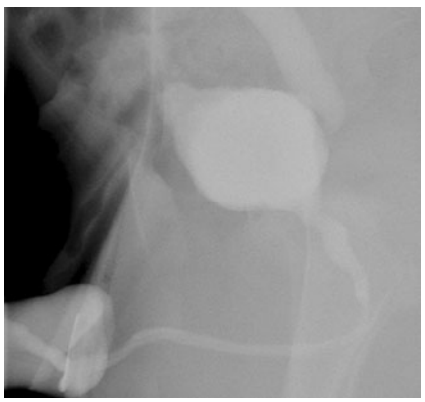

Fig. 1 Micturition cystourethrogram in an infant boy showing the flushing of his prepuce

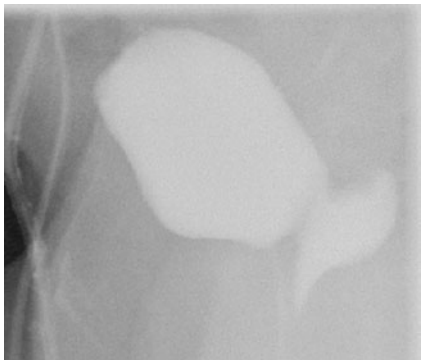

Fig. 2 Micturition cystourethrogram in an infant girl showing the flushing of her vagina

be virtually impossible to dismiss the leucocyturia and bacteriuria as ABU. The child will have to be treated and followed-up as a case of febrile UTI.

Based on the epidemiology data described above, one out of every four infant boys and one out of every six infant girls with true bacteriuria and fever will actually have ABU and/or another infection but be wrongly be diagnosed as a patient with febrile UTI. The chance of contaminated cultures will increase the number of false positive diagnosis to between 7.5 and 62.8% if SPA cultures are not used to verify the diagnosis.

These potential discrepancies can help to explain the sometimes confusing data that exist regarding different aspects of febrile UTI in children. One such confusing factor is the biologically unlikely finding that the number of

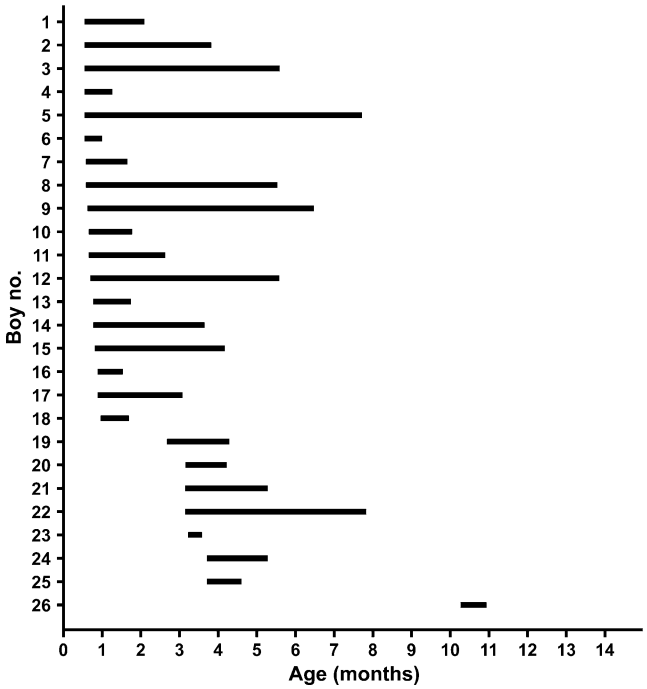

Fig. 3 Asymptomatic bacteriuria in infant boys verified by suprapubic aspiration

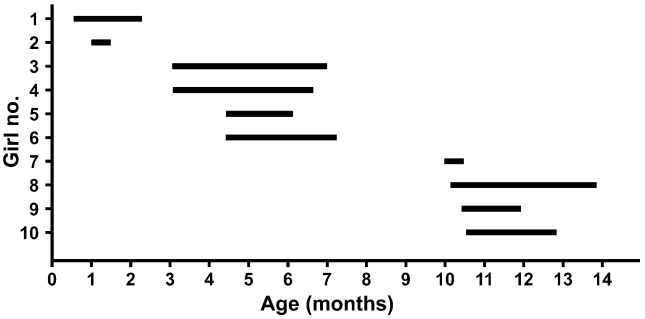

Fig. 4 Asymptomatic bacteriuria in infant girls verified by suprapubic aspiration

infants with proven kidney involvement by an uptake defect, based on the results of dimercaptosuccinic acid (DMSA) scanning in most studies, is lowest in the youngest age group. One study found that only 49% of infants diagnosed with a febrile UTI showed an uptake defect in at least one kidney compared to 73% in children between 1 and 4 years and 81% in children >5 years [18]. The rate of scarring defined as an uptake defect on the 6-month DMSA scan was also lower among the infants: 28 vs. 37 and 53% in the two older age groups, respectively.

The results of studies in infantile febrile UTI run the risk of being diluted and sometimes difficult to use because of the children with false positive diagnosis. This is true for studies such as those on inflammatory markers and the rate of vesicoureteric reflux. Six studies have recently been published on antimicrobial prophylaxis for the prevention of recurrent UTI in infants and children with vesicoureteric reflux [19–24]. Three of these studies used mainly suprapubic aspiration or bladder catherisation [19–21], while the others relied on bag collection of urine [22–24]. A difference in the rate of recurrent UTI between the children receiving antibiotics and the children who did not was found only in two of the studies that used the more accurate urine collection methods [19, 20]. It is known that enrolling children in a study who are not correctly diagnosed, possibly due to a contaminated urine test, can dilute the study results and give a false negative study result.

What should be done when planning further studies?

The most accurate method possible to collect urine in each age group should be used. In studies of febrile UTI, several different measurements of systemic inflammation, including C-reactive protein and procalcitonin, should be performed in all children. If children with low CRP and procalcitonin values are included in the study, then data should be presented for both groups of children.

Children with a pure growth of bacteria in the urine, but with bacterial numbers below the cut-off levels that are

normally used, for whom other clinical criteria from the urine test support a diagnosis of a UTI should not be excluded from the study but be presented as a separate arm. Circumcision greatly reduces both the risk for recurrent UTI and for preputial contamination, and the results should thus be presented separately for boys who are not circumcised and those who are.

Alternative diagnoses should not be excluded, particularly in febrile infants. A search for respiratory viruses as a possible cause of the increased temperature and leucocyturia should be performed with PCR. Such testing will help to distinguish children with fever and asymptomatic bacteriuria (ABU) from children with a true febrile UTI.

In clinical practice and in clinical studies, there will always be a number of children for whom it is not possible to obtain optimal urine cultures or to perform all relevant additional diagnostic tests. Analysing the data separately for children with and without optimal diagnostic studies can be one way to further our understanding of these issues.

In summary, there are several reasons why scientific and clinical knowledge on infantile febrile UTI is still so confusing. These include both false negative and positive diagnoses due to contamination of the specimen, other febrile infections in children with pre-existing asymptomatic bacteriuria and problems arising from which bacterial number constitutes a "true" UTI. Further studies to clarify the treatment management of children with a UTI will need to take the issues discussed above into consideration.

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