Arch Pediatr Infect Dis. 2015 April; 3(2): e21386. DOI: 10.5812/pedinfect.21386

Published online 2015 April 15. **Review Article**

Diagnostic Challenges in Urinary Tract Infections in Children

Mostafa Sharifian [1,*]; Shakiba Sharifian [1]

[1]Pediatric Nephrology Research Center (PNRC) and Pediatric Infections Research Center (PIRC), Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

[*]*Corresponding author*: Mostafa Sharifian, Pediatric Nephrology Research Center (PNRC) and Pediatric Infections Research Center (PIRC), Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran. Tel: +98-2122226941. Fax: +98-2122220254, E-mail: Sharifian.dorche@gmail.com

Received: June 21, 2014; **Revised:** September 8, 2014; **Accepted:** September 26, 2014

Context: Urinary tract infections (UTIs) are among the most common infections in children that affect up to 3% of boys and 8% of girls. Delay in diagnosis and treatment causes renal injury and scars that can progress to end stage renal disease (ESRD) requiring dialysis and transplantation.

Results: There are many pitfalls in diagnosis of UTIs both with urinalysis and culture methods and also in evaluating the risk factors and causes of UTIs.

Conclusions: This paper reviews and discusses the common pitfalls in diagnosis and evaluation of UTIs in children.

Keywords: Urinary Tract Infection; Renal Disease; Diagnosis; Children

1. Context

Urinary tract infections (UTIs) are one of the most common diseases in children that affect up to 3% of boys and 8% of girls (1-4). Urinary tract infections if missed or left untreated can lead to renal scar and hypertension which can be malignant and severe enough to cause hypertensive encephalopathy (5). Also, delay in treatment encompasses more scars that can progress to end stage renal disease (ESRD) requiring dialysis and transplantation (6). For prompt treatment, we need prompt and early diagnosis. There are many pitfalls in diagnosis of UTIs.

2. Pitfalls in Diagnosis of Urinary Tract Infections

2.1. Urinalysis

Leukocyturia is considered as one of the critical findings in UTIs, while if the urine is dilute and stays at room temperature for a while the leukocytes will lyse and there will be no significant amount of white blood cells (WBC) in the urine in the presence of true UTIs. On the other hand, there are many conditions in which urine contains a significant amount of leukocytes but without infection (Table 1 lists these situations (4)). Among these conditions, interstitial nephritis (IN) is common; when there is high probability of IN, the urine sediment can be stained with Wright or Geimsa and many eosinophil will be detected.

2.2. Nitrite Test

This is a very sensitive test which turns positive even in the presence of low amounts of nitrite in the urine but bacteria that reduce nitrate to nitrite need four hours of bladder time, while a child who suffers from UTIs, especially cystitis, may void every 15 minutes, (even a normal infant may void hourly and toddlers normally void 11 times/24 hours). In this situation the bacteria do not have the opportunity to reduce urine nitrate to nitrite turning the dipstick to positive; thus the sensitivity of the nitrite test in children is around 30%, however specificity in girls and circumcised boys is more than 90% (1). In uncircumcised boys a drop of urine may persist under the prepuce after urination; skin micro-organisms change urine nitrate to nitrite turning the very sensitive dipstick to positive thus giving false positive results. Uncircumcised boys have greater probability to be falsely diagnosed with UTIs and also greater probability of true UTIs.

Table 1. Clinical Conditions That May be Associated With Sterile Pyuria

Partially Treated UTIs	Hydronephrosis
Interstitial nephritis	appendicitis
Renal tubular acidosis	dehydration
Glomerulonephritis, especially acute post infectious glomerulonephritis	meatal or urethral irritation, especially in males
Renal cystic diseases	vaginitis in females
Renal stone disease	renal tuberculosis

2.3. Urine Culture

Urine culture is the gold standard for UTI diagnosis but

again it has many pitfalls. Firstly, urine culture results are usually not reliable for a specimen obtained by a urine bag as these containers can be contaminated by feces or perineal normal flora (1, 2); this is less likely to occur with specimens obtained by a catheter and almost never happens with suprapupic aspiration of urine samples. Some references prefer catheter specimens (1) and some prefer suprapubic aspiration (2) and in our country most parents, don't accept neither catheter nor suprapubic puncture, perhaps because they underestimate the drawbacks of missing a UTI in small children i.e. future hypertension and renal failure. The subject of colony count is also a matter of debate and controversy. While a colony count of 103 in specimens obtained by midstream urine (MSU), in a pregnant woman is indicative of a UTI based on the importance of infection during pregnancy, many references suggest a colony count of 105 as an indication of UTI in MSU for other situations.

It is widely accepted that many microorganisms need about 20 minutes of bladder time to double, thus if the infected urine remains in the bladder through out the night, the first morning specimen will show 105 colonies of invading agents but again the infant voids at least every hour and older children void at even a shorter time when having a UTI and a component of cystitis, resulting less colony count in the case of severe pyelonephritis. Another factor that affects colony count is urinary specific gravity (SG) if urine is very dilute, which is frequent in pyelonephritis and reflux or obstructive uropathy such as posterior urethral valves (PUV); in this case there is an interstitial nephritic and tubulopathy and frequently, low colony count in the presence of severe pyelonephritis and reflux nephropathy. In specimens obtained by suprapubic aspiration it has been suggested that a few colonies of gram positive organisms are compatible with UTIs, still it depends on the physician to decide to diagnose the patient as having a UTI, especially if there is no obvious clinical manifestations.

2.4. Imaging Studies

There is controversy regarding whether imaging studies are needed after the first UTI and again what kind of imaging is required. Based on the National Institute for Health and Care Excellence (NICE protocol) (7) and also the American Academy of Pediatrics (AAP) there is no need for imaging studies in children beyond six months of age for the first UTI (8), but as described by the author (9), we face many situations where the parents do not remember any kind of urinary signs or symptoms and the child has multiple renal scars and hypertension and even hypertensive encephalopathy as the result of missing several episodes of UTIs.

In imaging studies, ultrasound (U/S) is a well-known operator-dependent method. Voiding cysto-urethrography (VCUG) has lower sensitivity in detecting a vesicoureteral reflux (VUR), as it is a static process and takes a picture of the urinary system once, at the time of exposure. However, it can image a detailed anatomy of the urinary tract. Direct radionuclide cystography (DRNG) however has high sensitivity in detecting VUR but does not show the detailed anatomy. On the other hand VCUG and DRNG both need catheterization and have a significant radiation burden; many parents are unsatisfied and do not agree for catheterization and of course the physician has radiation concerns for an adolescent girl even when there is recurrent UTIs and evidence of bladder dysfunction. Dick PT and Feldman W in an evaluation of 434 publications through a systematic overview concluded that the current recommendations are not based on firm evidence (10). Many authors have to find a better way for detecting VUR and reduce invasiveness of the procedures (11-14).

We found evidence for extensive efforts in the medical literature trying to diagnose VUR without radiation and catheterization. One of the most interesting is to analyze acoustic alarms during voiding (15).

The author tried to potentiate the sound which is created during urination from turbulence of urine when there is VUR. The authors found that this test detected VUR in 35 of 37 patients with VUR and no VUR in 16 out of 17 individuals without VUR, thus the high sensitivity and specificity still suggests that VCUG is the gold standard for diagnosing VUR.

In another effort Assadi (16), Sharifian et al. (17) and Kaminska et al. (18) tried to diagnose VUR without catheterization and radiation by measurement urinary beta 2 microglobulin (B2MG); this test was sensitive only for high grade VUR in all three studies. Ultrasound study (U/S) after filling the bladder with levovist, a U/S sensitive contrast, could help diagnose VUR (19), yet it requires catheterization and has low sensitivity and specificity. In detection of renal involvement and confirming pyelonephritis, none of the acute phase reactants such as leukocytes in blood, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) or leukocyte in urine or detection of antibody coated bacteria are considered reliable in diagnosis of renal involvement. but di-mercapto succinic acid scan (DMSA) (3, 4); Which has a high burden of isotope radiation, this is because the protocol of bottom-up and top down is introduced in recent years (7).

In diagnosis of pyelonephritis there has been many diagnostic trials to validate urinary biomarkers such as interleukin 1 and 6 (20), interleukin 8 (21), tumor necrosis factor-alpha (22), adrenomedullin (23-25) and endothelia 1 (26). Although they could help in diagnosis of pyelonephritis, these tests are expensive and not available in routine practice and still DMSA scan is the gold standard.

When physicians face a pyelonephritis especially in a small child we suggest the use of U/S straight away and if the results are abnormal, VCUG can be used based on the bottom up policy and if U/S is normal then, DMSA scan is needed to see whether renal injury has developed or not. However, if U/S is normal and the physician is concerned

about renal scars a DMSA scan should be done at the time of acute illness or six months later based on the patient and their family situation, and at this time if there is severe renal tissue involvement, then VCUG or DRNC or MRU may be indicated.

3. Discussion

Diagnosis, evaluation and management of UTIs are highly controversial and this is the responsibility and art of the physician to choose shorter and better ways to tackle the patients' problems.

Acknowledgements

We appreciate the cooperation of the research committee of the Pediatric Infections Research Center, Shahid Beheshti University of Medical Sciences, for their contribution.

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