

Optimising paediatric urinary tract infection diagnosis

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Urinary tract infection (UTI) is the most common cause of serious bacterial illness among children and infants.¹ Up to 2% of boys and 8% of girls will develop at least 1 episode of UTI by the age of 7 years.^{1,2} Of these, it is estimated that 12% to 30% will experience recurrence within a year.³ While majority of patients recover without any long-term sequelae, UTIs can lead to severe complications such as kidney scarring and sepsis if not diagnosed and treated promptly. A very small proportion of children will develop kidney failure from UTI which is typically a result of recurrent UTIs. Known risk factors for UTI among children include female sex, age and the presence of conditions that affect urine flow, such as vesicoureteric reflux or urinary stasis (neurogenic bladder, constipation).⁴ UTI, typically develops due to the ascension of uropathogens that colonise the periurethral regions to the bladder (cystitis), which may ascend further up the urinary tract (pyelonephritis) and lead to bloodstream infection (urosepsis). UTIs from haematogenous spread is possible, although uncommon. Common pathogens implicated are gram-negative bacteria—primarily *Escherichia coli*; however, other pathogens such as *Klebsiella*, *Proteus* and *Enterobacter* can also be involved.

The clinical presentation of UTI, especially among infants, can be variable and is often non-specific. As such, diagnosis of UTI can be challenging, particularly among younger children, owing to the lack of localising symptoms. As such, UTI is suspected in every febrile infant with or without urinary symptoms. This is particularly important as prompt treatment of UTI significantly reduces the risk of kidney scarring if treated within 24–48 hours from the start of the febrile illness.⁵ While a positive urine culture from an appropriately taken sample is the gold standard for UTI diagnosis,⁶ turnaround of urine cultures can take between 24 and 48 hours which may delay decision for treatment. As such, physicians routinely commence empiric UTI treatment based on clinical symptoms and results from urinalysis.

The detection of urinary leukocyte esterase (an enzyme present in white blood cells [WBCs]) and nitrites (conversion of nitrates by bacteria) in combination with detection of WBCs in urine microscopy are used to determine the likelihood of UTI among children. Previous studies have shown that the inclusion of urine microscopy for the detection of WBC among urine samples improves the sensitivity of the test due to the direct visualisation of cells in the urine sample that do not degrade over time.^{7,8} In a study comparing a point-of-care urinalysis (POCT) and laboratory performed urinalysis involving 42,452 urine specimens from children presenting to the emergency department, the improved sensitivity of the laboratory-performed urinalysis (89.1% confidence interval [CI] 86.4–88.8 versus 82.5% CI 79.4–85.3) was driven by the sensitivity of WBC detection on microscopy.⁸ Even so, there remains no consensus on the optimal WBC threshold to accurately predict UTIs on urinalysis, leading to variability in clinical practice and the risk of either over- or under-treatment.

In the accompanying study published in this issue of the *Annals*, researchers from KK Women's and Children's Hospital, Singapore, proposed to investigate the optimal urine WBC threshold for predicting UTIs among children being evaluated in the emergency department.⁹ This prospective observational study recruited 1188 participants <18 years old over a 10-month period who were screened for suspected UTI. The authors reported that a urinalysis WBC threshold of $\geq 100/\mu\text{L}$ was associated with an overall sensitivity of 82.2% and a negative predictive value (NPV) of 86.2% for detecting UTI. However, an estimated 17.3% of culture-positive UTIs would be missed, particularly among nitrite-negative samples which often occur in younger children. As expected, lowering the WBC threshold to $\geq 10/\mu\text{L}$ increased the sensitivity and NPV to 96.5%, and 94.1%, respectively, but with an expected absolute increase in the number of urine cultures of 419 over a 12-month period and a likely increase in inappropriate antibiotics exposure.

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The study underscored the high proportion of nitrite-negative UTIs (278/460, 60.4%), particularly among infants under 1 year of age. Although majority of enteric gram-negative organisms would be able to reduce nitrates to nitrite; this conversion may not occur in young children due to their frequent bladder emptying, which limits the time needed for nitrate conversion to occur hence lack of urinary nitrite detection in young children with UTI.¹⁰ Among the nitrite-negative samples, lowering the WBC threshold from 100/ μ L through to 10/ μ L significantly reduced the rate of missed UTIs from 17.3% to 2.2%, highlighting the potential for adjusting WBC in selected clinical context to increase the sensitivity for UTI detection. It is important to note that the current workflow in this study involves a screening POCT (dipstick) which would reflex to a laboratory-based urinalysis if the screen is positive for leukocyte esterase or nitrite. Many clinical settings may not have the capacity or setup to conduct both tests before deciding on empiric coverage.

This study provides valuable clinical evidence that could influence clinical guidelines and practice. As noted in the current publication, various studies performed in different countries have suggested a range of optimal WBC counts for diagnosis of UTI—ranging from $\geq 25/\mu$ L to $\geq 50/\mu$ L. Interestingly, when comparing similar ranges of WBC counts in this study to the aforementioned studies in different countries, the sensitivity remains similar but the specificity is notably lower. The findings of this study also suggest that while a higher threshold ($\geq 100/\mu$ L) may reduce the number of unnecessary urine cultures and antibiotic prescriptions, it carries a significant risk of missing UTIs, particularly in nitrite-negative cases.

The balance between sensitivity of testing for empiric UTI treatment and resource utilisation continues to present a significant dilemma in the care of children who present with undifferentiated symptoms. The results from this study provide important data that can aid the clinician in tailoring their diagnostic approach based on a patient's risk factors and clinical presentation. This is especially true among young patients that are likely to present with nitrite-negative UTIs as well as in settings where the risk of missed UTIs may result in severe consequences. The use of a lower WBC threshold

may be justified in spite of the anticipated increase in urine cultures and empiric antibiotic treatment.

While further studies may be required to understand various combinations of factors that can affect diagnostic accuracy, this study's findings provide a basis for the development of algorithms that can incorporate various parameters to improve diagnostic accuracy of UTI. The ultimate goal is to facilitate more accurate and timely treatment of UTIs in children, thereby reducing the risk of complications.

Declaration

The authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: emergency medicine, paediatrics, urinary characteristics, urinary tract infection, urinary white blood cells

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