

Investigating urinary characteristics and optimal urine white blood cell threshold in paediatric urinary tract infection: A prospective observational study

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ABSTRACT

Introduction: While the definitive diagnosis of urinary tract infection (UTI) requires a positive urine culture, the likelihood of UTI can be determined by urinalysis that includes white blood cell (WBC) count. We aimed to determine the optimal urine WBC threshold in urinalysis to predict UTIs in children presenting at the emergency department (ED).

Method: We performed a prospective observational study in the ED at KK Women's and Children's Hospital for children below 18 years old who underwent both urine microscopy and urine cultures, between 10 January and 7 November 2022. We assessed the various urine WBC thresholds associated with culture-proven UTIs using sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and area under receiver operating characteristic curve.

Results: We found a culture-proven UTI rate of 460/1188 (38.7%) among all patients analysed, and 278/998 (27.9%) among those with nitrite-negative urine samples. Among all patients, a urinalysis WBC threshold of 100/ μ L had a sensitivity of 82.2% (95% confidence interval [CI] 78.4–85.5) and negative predictive value of 86.2% (95% CI 83.6–88.4). Among those who were nitrite-negative, a WBC threshold of ≥ 100 / μ L resulted in a potential missed rate of 48/278 (17.3%). By lowering the WBC threshold to ≥ 10 / μ L, the potential missed cases reduced to 6/278 (2.2%), with an estimated increase in 419 urine cultures annually.

Conclusion: A urine microscopy WBC threshold of ≥ 100 / μ L results in a clinically significant number of missed UTIs. Implementation of various thresholds should consider both the potential missed UTI rate and the required resource utilisation.

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

CLINICAL IMPACT

What is New

- This study aims to determine the optimal urinalysis white blood cell (WBC) threshold associated with urinary tract infection (UTI) in the paediatric population.

Clinical Implications

- The previous urinalysis WBC threshold of ≥ 100 / μ L may potentially miss about 17% of paediatric UTI.
- This study provides data on missed UTI rates and the corresponding increase in investigations at each urinalysis WBC threshold, to help clinicians determine the optimal threshold in their practice.

INTRODUCTION

Urinary tract infection (UTI) is a common diagnosis in the paediatric emergency department (ED). It accounts for an estimated 5–14% of paediatric ED visits yearly in the US.¹⁻³ It is a common cause of serious bacterial infections in children, and the most common microorganism is *Escherichia coli* (65–75%), followed by *Klebsiella pneumoniae* (23%) and *Proteus mirabilis* (7%).⁴⁻⁷ Although older children may present with specific urinary symptoms, young children may present with non-specific complaints, including fever without localising symptoms, poor feeding, vomiting or irritability, which make prompt diagnosis of UTI challenging.^{1,8}

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The gold standard for UTI diagnosis is a positive urine culture from a clean catch midstream or an in-out catheterisation urine sample, which requires 24 to 48 hours turnaround time in most places.^{7,9} Therefore, physicians are required to make an informed decision on empirical treatment for UTI based first on clinical assessment and results from urinalysis, while awaiting urine culture results. While there is a clear need to avoid missing UTIs, which place patients at risk of urosepsis and long-term kidney impairment and scarring, overtreatment can result in antimicrobial resistance in the long term.¹⁰ Moreover, prompt initiation of UTI treatment is vital because the odds of kidney scarring are 74% lower in children who receive treatment within 24 hours from the onset of fever, compared to those who receive treatment after 72 hours of fever.^{5,6}

To predict UTI, physicians consider urinary white blood cell (WBC) count, urine nitrite positivity and other urinary characteristics from the urinalysis. Unfortunately, there is no international consensus on the best WBC cut-off value in urinalysis to diagnose a likely UTI for which clinicians should prescribe empirical antibiotics.

Therefore, we aimed to investigate urinary characteristics, and to determine the optimal thresholds of urine WBC and other urinalysis parameters to predict the diagnosis of UTI.

METHOD

Study setting and design

We performed a prospective observational study in the children's ED at KK Women's and Children's Hospital in Singapore over 10 months, from January 2022 to November 2022. Our centre is 1 of 2 tertiary paediatric hospitals in the country, with an annual ED attendance of about 150,000 children. This study was approved by the Centralised Institutional Review Board with waiver of informed consent (CIRB 2023/2124).

Inclusion and exclusion criteria

We included children <18 years old, who were screened for suspected UTI. We followed existing guidelines for UTI screening, which includes patients with:

- Urinary symptoms (dysuria, haematuria, increase urinary urgency/frequency, dribbling, oliguria/anuria)
- Febrile illness with vomiting
- Febrile illness without any localising symptoms
- Increased irritability in non-verbal children
- Non-febrile infants <3 months old with non-specific or urinary symptoms including irritability, foul-smelling urine, or haematuria

- High risk of UTI (recurrent UTIs, kidney, spinal or genitourinary structural abnormalities) and symptomatic

We excluded following groups of patients:

- Children who had antibiotic pretreatment within 2 weeks of urine collection, and children who were on uroprophylaxis; in both these scenarios, the microscopy would not be accurate for interpretation and the urine culture may be falsely negative
- Cases where the urine samples were insufficient to send for both urine culture and urine microscopy
- Febrile infants <3 months old, because this is a high-risk group that would be hospitalised and subsequently receive extensive investigations
- High risk of UTI but asymptomatic (likely asymptomatic bacteriuria)

Testing procedures

At the children's ED, the first-line screening test is the urine dipstick (Combur 10 Test Strips, Roche Diagnostics, Rotkreuz, Switzerland). If the initial urine dipstick was $\geq 2+$ positive for leukocyte esterase and/or positive for nitrite, a midstream or in-out catheterisation urine sample was collected and sent to the hospital's laboratory for urinalysis, including urine microscopy. As part of this study, we required that urine samples be concurrently sent for urine culture. Midstream urine samples were collected by the respective caregivers after being taught the proper method of collection by the attending physicians and/or nurses, while in-out catheterisation urine samples were performed by physicians.

Urinalysis was performed on uncentrifuged urine samples at the hospital's Clinical Chemistry Laboratory. Urine was first tested using Combur 10 Test Strips (Roche Diagnostics) that were read on a Cobas u 411 urine analyser (Roche Diagnostics). When the test strip results for either red blood cells (RBCs), WBCs, nitrite or protein were positive, urine microscopy was performed on Kova Glasstic slides (Kova International, CA, US), and cells were manually counted by the lab personnel. Urine cultures were performed at the hospital's microbiology laboratory. During office hours, fresh urine was plated onto blood and MacConkey agar using calibrated 1 μ L plastic loops; agar plates were incubated at 35°C overnight. After office hours, urine was inoculated at the ED onto Uricult Trio dipslides (Orion Diagnostica, Espoo, Finland), which consist of cystine-lactose-electrolyte-deficient (CLED), MacConkey and *Escherichia coli* media, before it was sent to the laboratory to be incubated at 35°C overnight.

In our institution, at the time of study, we were using a WBC threshold of $\geq 100/\mu\text{L}$ in a mid-stream or in-out catheterisation urine microscopy sample to initiate treatment for UTI, empirically with a course of cephalexin, while awaiting the urine culture result.¹¹

Data variables and definitions

We collected information on patient demographics, presenting symptoms including urinary symptoms or symptoms commonly associated with UTI, and significant past medical history including previous UTI, and kidney, spinal or genitourinary structural abnormalities.

We obtained the following information from ED urine dipstick screening: leukocyte, erythrocyte and protein semiquantitative counts. Laboratory urine microscopy and urinalysis results were documented for RBCs and WBCs as cells per microliter, as well as the presence (or absence) of microorganisms and nitrite positivity.

In our study, we defined UTI as the presence of a uropathogen in urine by culture, with at least 50,000 colony-forming units (CFUs)/mL in catheterised urine samples as per the revised 2011 American Academy of Paediatrics guideline; or >105 CFU/mL in clean-catch midstream urine samples as per the 2012 Italian Society of Paediatric Society, the 2015 European Association of Urology and European Society for Paediatric Urology guidelines, and the 2016 Urological Association of Asia and Asian Association of Urinary Tract Infection and Sexually Transmitted Infection guidelines.^{10,12,13} In the case of growth of dual uropathogens, we considered a diagnosis of UTI when both the uropathogens had significant growth as defined above.

Nitrite-positivity, irrespective of the urine WBC counts, is specific for UTI.¹² Therefore, we performed a sensitivity analysis among those with nitrite-negative UTIs.

Statistical analysis

We described continuous variables using mean with standard deviation (SD) or median with interquartile range (IQR), depending on normality. Categorical variables were described using frequencies and percentages. We compared children with a diagnosis of UTI to those without a diagnosis of UTI. We used either t-test or Wilcoxon rank sum test for continuous data depending on normality, and chi-square test for categorical data. We took statistical significance at $P < 0.05$. All P values were based on 2-tailed tests. We reported the area under receiver operating characteristics (AUC) curves using point estimates with 95% confidence intervals

(CIs). The optimal WBC threshold corresponded with the point nearest to the upper left corner of the AUC box, therefore providing the values of highest sensitivity and specificity. At each threshold, we evaluated performance using sensitivity, specificity, negative and positive predictive values, and positive and negative likelihood ratios. Among those with nitrite-negative urine, we performed a subanalysis on infants, defined as <1 year old because this group tends to present with non-specific symptoms. Statistical analysis was performed using SPSS version 26 (IBM Corp, Armok, NY, US).

RESULTS

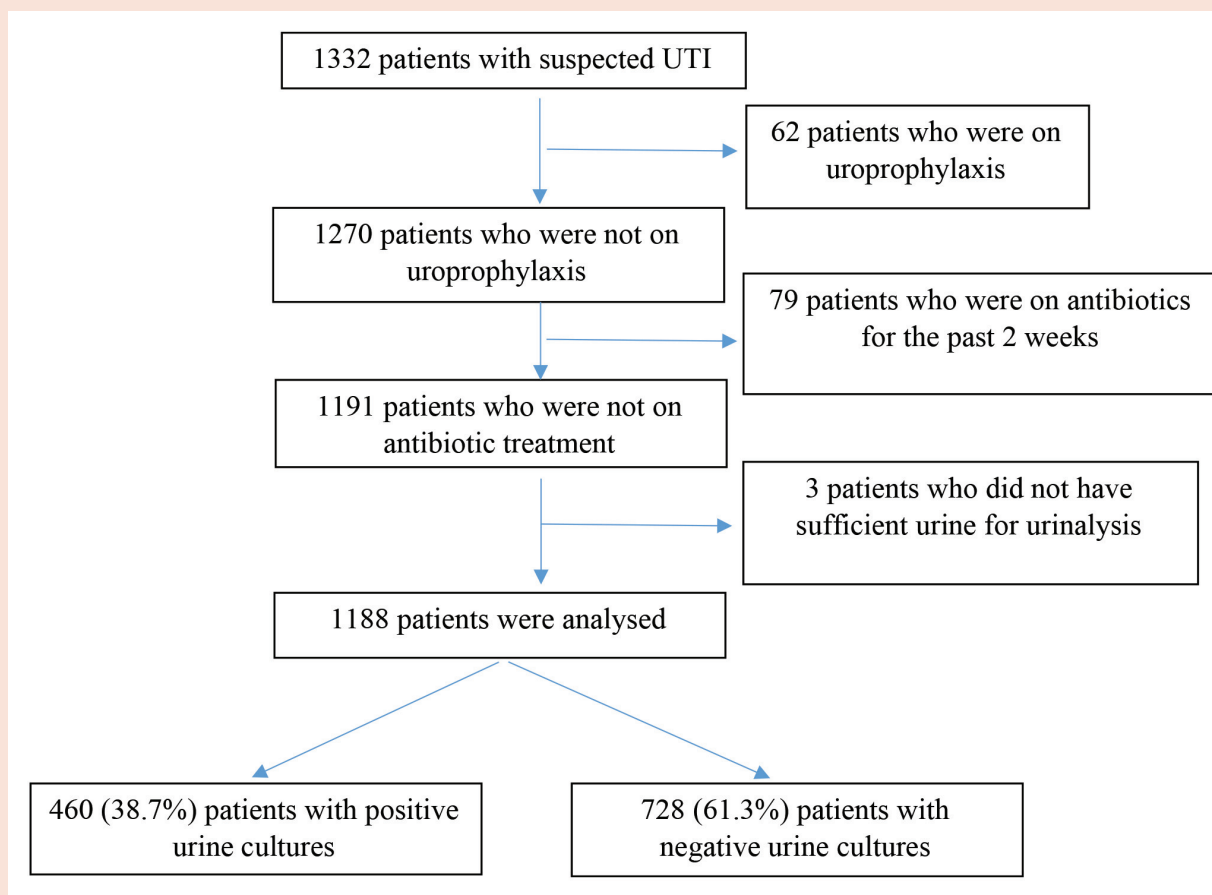
A total of 1188 urine samples from 1188 patients were analysed. Among them, 460 (38.7%) were diagnosed with UTI (Fig. 1). Our patients had a median age of 3 years (IQR 1.0–6.0) and a median weight of 14.3 kg (IQR 9.8–22.6). There was a greater number of males in the group with UTI compared to the group without (164/460, 35.7% versus [vs] 162/728, 22.3%, $P < 0.001$) (Table 1). Among infants ≤ 3 months old, this male predominance was more marked (29/38, 76.3% vs 9/38, 23.7%). Those with a significant past medical history such as previous UTI and structural abnormalities were at higher risk of getting a UTI.

Children with UTIs had significantly higher WBC and RBC on urine microscopy compared to those without (median WBC were 604 WBC/ μL [IQR 170–2000] vs 27 WBC/ μL [IQR 4–129], $P < 0.00$; and median RBC were 27 RBC/ μL [IQR 10–70] vs 7 RBC/ μL [IQR 0–28], $P < 0.001$) (Table 2). There was a significantly higher proportion of those with raised urine protein, as well as presence of urine nitrite and microscopically visible microorganisms among children with UTIs compared to those without UTIs (Table 2). The urine WBC had an AUC of 0.83 (95% CI 0.81–0.86) in the prediction of UTI, while urine RBC had an AUC of 0.69 (95% CI 0.66–0.72).

Among the 460 patients with positive urine culture results, 446 (97%) had a single uropathogen, and 14 (3%) had 2 uropathogens, with significant growth that fulfilled the diagnosis of UTI as defined above (Table 3). The top 3 most common microorganisms found were *Escherichia coli* (80%), *Proteus mirabilis* (10%) and *Klebsiella pneumoniae* (5.2%). Thirty-one (7%) of the microorganisms were positive for extended-spectrum beta-lactamases (ESBLs).

Among the 460 culture-proven UTIs, 278 urine specimens were nitrite negative, among which 113/278 (40.6%) were <1 year old. The AUCs of various WBC thresholds in all patients with UTI, and in patients with nitrite-negative UTI are

Fig. 1. Flow chart for study population.



shown in Fig. 2(A) and Fig. 2(B). A urinalysis WBC threshold of 100/ μ L had an ROC of 0.76 (95% CI 0.73–0.79) and 0.77 (95% CI 0.74–0.80) for all patients and nitrite-negative patients, respectively. Among all patients, a urinalysis WBC threshold of 100/ μ L had a sensitivity of 82.2% (95% CI 78.4–85.5) and negative predictive value (NPV) of 86.2% (95% CI 83.6–88.4) (Table 4). By lowering the threshold to 10/ μ L, we could achieve a sensitivity of 96.5% (95% CI 94.4–98.0) and a NPV of 94.1% (95% CI 90.6–96.3). Among nitriteneutral urine samples, thresholds of 100/ μ L, 50/ μ L and 10/ μ L would have missed 48/278 (17.3%), 35/278 (12.6%), and 6/278 (2.2%) UTIs, respectively (Table 5[A]). At the same time, lowering the threshold from 100/ μ L would result in an estimated annual increase in 130 (for a threshold of 50/ μ L) and 419 (for a threshold of 10/ μ L) urine cultures, respectively, with the same number of children being started on empirical antibiotics (Table 4). Among infants with nitrite-negative UTI, a urinalysis WBC threshold of 100/ μ L had a sensitivity of 78.8% (95% CI 70.1–85.9) and NPV of 77.1% (95% CI 69.8–83.1). By lowering the threshold to 10/ μ L, we could

achieve a sensitivity of 96.5% (95% CI 91.2–99.0) and a NPV of 92.7% (95% CI 82.6–97.2) (Table 5[B]). Among these samples, thresholds of 100/ μ L, 50/ μ L and 10/ μ L would have missed 24/113 (21.2%), 17/113 (15.0%), and 4/113 (3.5%) UTIs, respectively.

In our study, 247 out of 460 patients (53.7%) with UTI had kidney imaging on follow-up, while 213 of them (46.3%) either declined kidney imaging or were lost to follow-up. Among those who had kidney imaging, 26/247 (10.5%) had abnormal structures, including solitary or duplex kidneys, pelvicalyceal dilatation, dilated ureters, or small kidneys. Among children with recurrent UTIs for whom micturating cystourethrogram (MCUG) had been performed, 10/12 (83.3%) had vesicoureteral reflux.

DISCUSSION

We performed a prospective observational study to examine urinary characteristics and to evaluate the optimal WBC threshold in predicting UTI. The UTI prevalence was 38.7% in this study population, and the most common organisms were *Escherichia*

Table 1. Baseline characteristics of study population.

Variable	No UTI n=728	UTI n=460	P value
Age in years, median (IQR)	3.0 (1.0–7.0)	1.0 (0.7–5.0)	<0.001
Age ≤3 months, no. (%) ^a	38 (5.2)	38 (8.3)	-
Age >3 months to 2 years, no. (%)	258 (35.4)	241 (52.4)	-
Age >2 years to 8 years, no. (%)	315 (43.3)	136 (29.6)	-
Age >8 years to 18 years, no. (%)	117 (16.1)	45 (9.8)	-
Male sex, no. (%)	162 (22.3)	164 (35.7)	<0.001
Presence of past medical history, no. (%)			<0.001
Kidney/spinal/genitourinary structural abnormality	30 (4.1)	9 (2.0)	-
Previous UTI + structural abnormality	11 (1.5)	20 (4.4)	-
Fever >37.5°C vs afebrile, no. (%)			<0.001
Febrile	449 (61.7)	366 (79.6)	-
Afebrile	279 (38.3)	94 (20.4)	-
Urinary symptoms, no. (%)	275 (37.8)	207 (45.0)	0.044
Dysuria	180 (65.5)	132 (63.8)	-
Haematuria	39 (14.2)	18 (8.7)	-
Increased urinary frequency	27 (9.8)	10 (4.8)	-
Smelly urine	15 (5.5)	46 (22.2)	-
Urinary urgency	14 (5.1)	1 (0.5)	-
Vomiting (%)	31 (4.3)	103 (22.4)	<0.001
Loose stools, no. (%)	5 (0.7)	29 (6.3)	<0.001
Abdominal pain or tenderness, no. (%)	113 (15.5)	62 (13.5)	0.333
Presence of penile or per vagina complaints, no. (%)	23 (3.2)	13 (2.8)	0.744

IQR: interquartile range; UTI: urinary tract infection

^a Infants ≤3 months old with febrile illness were excluded in the study.

coli, *Proteus mirabilis* and *Klebsiella pneumoniae*. We reported the performance of various urinary WBC thresholds ranging 10–100/μL, the number of missed UTIs at each threshold, as well as the corresponding number of urine cultures that would be required.

The diagnosis of UTI requires a confirmatory urine culture, which is available only after 24–48 hours in most settings. A point-of-care urine dipstick is usually first performed, with a sensitivity of between 83–93%.^{1,6,10,14} If the urine dipstick fulfils the criteria for a possible UTI, the urine sample will then be sent to the laboratory for analysis. Therefore, urinalysis is key for early decision-making. Urinalysis has a reported sensitivity of predicting a likely UTI between 75–85%.¹⁵ The optimal WBC threshold

in predicting likely UTI is a topic of debate in the literature. Adult UTI studies in the Netherlands and Belgium reported the optimal cut-off to be in the range of 20–74 WBC/μL.^{16,17} In the paediatric population, studies in different countries have reported a range of WBC diagnostic thresholds: ≥25/μL in Taiwan (sensitivity 79%, specificity 87%); ≥35/μL in Belgium (sensitivity 99.5%, specificity 80.6%); and ≥50/μL in girls of all ages and boys under 3 years old, and ≥10/μL in boys above 3 years old in Germany.^{12,14,18} In our study, we found that our institution's existing threshold of urinary WBC ≥100/μL had the highest AUC (0.761, 95% CI 0.733–0.789), but sensitivity and negative predictive value were only moderate (83.4% and 91.7%, respectively).

Table 2. Laboratory-tested urine microscopy and urinalysis findings.

Variable	No UTI n=728	UTI n=460	P value
Urine microscopy red blood cells (per µL), median (IQR)	7 (0–28)	27 (10–70)	<0.001
Urine microscopy white blood cells (per µL), median (IQR)	27 (4–129)	604 (170–2000)	<0.001
Urine protein, no. (%)			<0.001
Negative	95 (13.0)	9 (2.0)	-
1+	583 (80.1)	323 (70.5)	-
2+	30 (4.1)	87 (19.0)	-
3+	12 (1.6)	33 (7.2)	-
4+	8 (1.1)	6 (1.3)	-
Urine nitrite positive, no. (%)	8 (1.1)	180 (39.3)	<0.001
Presence of microorganisms in urine microscopy, no. (%)			<0.001
Negative	373 (51.2)	31 (6.7)	-
Occasional or few	318 (43.7)	189 (41.1)	-
1+	26 (3.6)	104 (22.6)	-
2+	11 (1.5)	84 (18.2)	-
3+	0 (0)	52 (11.3)	-

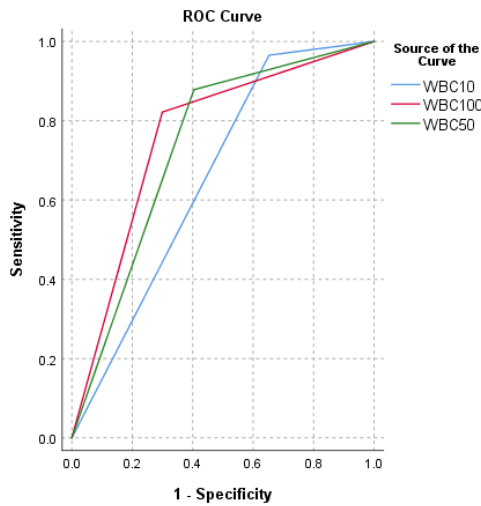
Table 3. Positive urine culture findings.

Variable	UTI n=460
Number of uropathogens	
Single uropathogen, no. (%)	446 (97)
2 uropathogens, no. (%)	14 (3)
Species of microorganisms, no. (%)	
Escherichia coli	371 (80)
Enterococcus faecalis	4 (0.08)
Enterobacter cloacae	1 (0.02)
Klebsiella pneumoniae	24 (5.2)
Proteus mirabilis	48 (10)
Others	27 (5.8)
Extended-Spectrum Beta-Lactamase positive microorganisms, no. (%) ^a	
Yes	31 (7)
No	429 (93)

^a ESBL microorganisms reported as per Calibrated Dichotomous Susceptibility guidelines, which are resistant to ampicillin, ceftazidime, ceftriaxone, cefotaxime and ceftazidime.

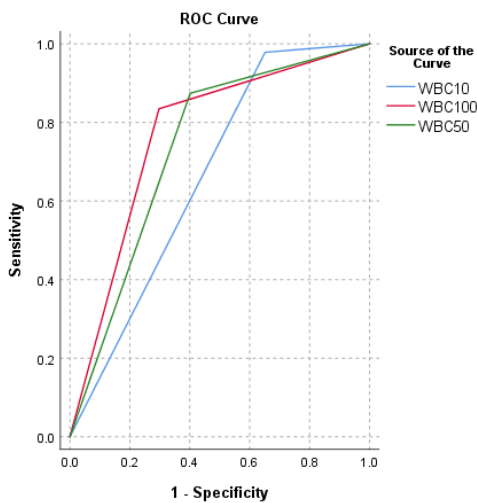
Fig. 2. Area under receiver operative characteristic curve (AUC) comparing different white blood cell thresholds in culture-proven urinary tract infection.

(A) AUC for all 1188 patients.



UFEME WBC thresholds	AUC (95% confidence interval)
WBC $\geq$ 100 (μL)	0.76 (0.73–0.79)
WBC $\geq$ 90 (μ L)	0.76 (0.73–0.79)
WBC $\geq$ 80 (μ L)	0.75 (0.73–0.78)
WBC $\geq$ 70 (μ L)	0.75 (0.72–0.78)
WBC $\geq$ 60 (μ L)	0.74 (0.72–0.77)
WBC $\geq$ 50 (μL)	0.74 (0.71–0.77)
WBC $\geq$ 40 (μ L)	0.73 (0.70–0.76)
WBC $\geq$ 30 (μ L)	0.72 (0.69–0.74)
WBC $\geq$ 20 (μ L)	0.69 (0.66–0.72)
WBC $\geq$ 10 (μL)	0.66 (0.63–0.69)

(B) AUC for all 988 patients with nitrite negative urine samples.



UFEME WBC thresholds	AUC (95% confidence interval)
WBC $\geq$ 100 (μL)	0.77 (0.74–0.80)
WBC $\geq$ 90 (μ L)	0.77 (0.74–0.80)
WBC $\geq$ 80 (μ L)	0.76 (0.73–0.79)
WBC $\geq$ 70 (μ L)	0.75 (0.72–0.79)
WBC $\geq$ 60 (μ L)	0.75 (0.72–0.78)
WBC $\geq$ 50 (μL)	0.74 (0.71–0.77)
WBC $\geq$ 40 (μ L)	0.73 (0.70–0.76)
WBC $\geq$ 30 (μ L)	0.72 (0.69–0.75)
WBC $\geq$ 20 (μ L)	0.70 (0.67–0.73)
WBC $\geq$ 10 (μL)	0.66 (0.63–0.70)

ROC: receiver operative characteristic; UFEME: urine full examination, microscopic examination; WBC: white blood cell

Apart from WBC count, presence of nitrite in the urinalysis is also one of the parameters to predict the diagnosis of UTI. Presence of nitrite, while helpful, may be falsely negative, because most Gram-negative enteric microorganisms need approximately 4 hours to convert dietary nitrate to nitrite.^{6,10,14} This is relevant especially for infants who empty their bladders rapidly.⁶ Furthermore, studies have shown that besides enterococcal UTI which usually produce nitrite-negative urine results, 96% of nitrite-negative UTI were due to more common gram-negative uropathogens, such as *Escherichia coli* (84%).¹⁹ In our

study, we presented the performance of the various urinalysis WBC thresholds in the overall population as well as in those with nitrite-negative urine samples.

Our study builds on the above literature by performing a sensitivity analysis of nitrite-negative urine samples. Among all children with nitrite-negative urine microscopy, we found that a WBC threshold of $\geq 100/\mu$ L missed 17.3% of UTI. By lowering the WBC threshold to $\geq 10/\mu$ L, the missed cases would be reduced to $<5\%$, with a sensitivity of 97.8% and a negative predictive value of 97.7%, but with a specificity of only 34.9%. Infants require more care,

Table 4. Comparing different white blood cell thresholds (all patients) in culture-proven urinary tract infections (n=1188).

UFEME WBC threshold to diagnose UTI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	NPV (%) [95% CI]	PPV (%) [95% CI]	Negative Likelihood Ratio [95% CI]	Positive Likelihood Ratio [95% CI]	Absolute total number of cultures over 10 months	Absolute increment in cultures (standardised to 12 months)
WBC ≥100 (µL)	82.2 [78.4–85.5]	70.0 [66.6–73.3]	86.2 [83.6–88.4]	63.4 [60.6–66.1]	0.25 [0.21–0.31]	2.74 [2.44–3.09]	622	Reference
WBC ≥90 (µL)	83.3 [79.5–86.6]	68.9 [65.5–72.3]	86.7 [84.1–88.9]	62.9 [60.2–65.6]	0.24 [0.20–0.30]	2.68 [2.3–3.0]	637	18
WBC ≥80 (µL)	83.7 [80.0–86.9]	66.9 [63.4–70.3]	86.7 [84.0–88.9]	61.5 [58.8–64.0]	0.24 [0.20–0.30]	2.53 [2.26–2.82]	654	39
WBC ≥70 (µL)	84.8 [81.2–87.9]	65.1 [61.5–68.6]	87.1 [84.4–89.4]	60.6 [57.9–63.1]	0.23 [0.19–0.29]	2.43 [2.18–2.70]	673	61
WBC ≥60 (µL)	86.1 [82.6–89.1]	62.6 [59.0–66.2]	87.7 [84.9–90.0]	59.3 [56.8–61.7]	0.22 [0.18–0.28]	2.30 [2.08–2.55]	698	91
WBC ≥50 (µL)	87.8 [84.5–90.7]	59.6 [55.9–63.2]	88.6 [85.7–90.9]	57.9 [55.5–60.2]	0.20 [0.16–0.26]	2.17 [1.98–2.39]	731	130
WBC ≥40 (µL)	90.0 [86.9–92.6]	55.8 [52.1–59.4]	89.8 [86.9–92.1]	56.2 [54.1–58.4]	0.18 [0.14–0.24]	2.03 [1.87–2.22]	771	179
WBC ≥30 (µL)	91.7 [88.8–94.1]	51.2 [47.5–54.9]	90.7 [87.8–93.1]	54.3 [52.3–56.3]	0.16 [0.12–0.22]	1.88 [1.74–2.04]	816	233
WBC ≥20 (µL)	93.9 [91.3–95.9]	44.8 [41.1–48.5]	92.1 [88.9–94.4]	51.8 [50.1–53.5]	0.14 [0.09–0.20]	1.70 [1.59–1.82]	879	308
WBC ≥10 (µL)	96.5 [94.4–98.0]	34.7 [31.3–38.3]	94.1 [90.6–96.3]	48.3 [46.9–49.7]	0.10 [0.06–0.16]	1.48 [1.40–1.56]	971	419

CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value; UFEME: urine full examination, microscopic examination; UTI: urinary tract infection; WBC: white blood cell

Table 5. Comparing different white blood cell threshold (nitrite negative) in culture-proven urinary tract infections.

(A) In all age groups (n=998).									
UFEME WBC threshold to diagnose UTI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	NPV (%) [95% CI]	PPV (%) [95% CI]	Negative Likelihood Ratio [95% CI]	Positive Likelihood Ratio [95% CI]	Number of missed UTI/ Total number of UTI (nitrite negative) (%)		
WBC ≥100 (µL)	83.4 [78.6–87.6]	70.3 [66.8–73.6]	91.7 [89.4–93.5]	52.0 [48.9–55.1]	0.23 [0.18–0.31]	2.85 [2.52–3.23]	48/278 (17.3)		
WBC ≥90 (µL)	84.2 [79.3–88.3]	69.2 [65.6–72.5]	91.8 [89.6–93.7]	51.3 [48.3–54.3]	0.23 [0.17–0.30]	2.73 [2.42–3.08]	44/278 (15.8)		
WBC ≥80 (µL)	84.9 [80.1–88.9]	67.1 [63.5–70.5]	92.0 [89.6–93.9]	49.9 [47.0–52.8]	0.23 [0.17–0.30]	2.58 [2.30–2.89]	42/278 (15.1)		
WBC ≥70 (µL)	85.6 [80.9–89.5]	65.3 [61.7–68.8]	92.2 [89.8–94.0]	48.8 [46.0–51.6]	0.22 [0.16–0.30]	2.47 [2.21–2.76]	40/278 (14.4)		
WBC ≥60 (µL)	87.1 [82.5–90.8]	62.8 [59.1–66.3]	92.6 [90.2–94.5]	47.5 [44.8–50.1]	0.21 [0.15–0.28]	2.34 [2.11–2.60]	36/278 (12.9)		
WBC ≥50 (µL)	87.4 [82.9–91.1]	59.9 [56.2–63.5]	92.5 [89.9–94.4]	45.7 [43.2–48.2]	0.21 [0.15–0.29]	2.18 [1.97–2.41]	35/278 (12.6)		
WBC ≥40 (µL)	89.9 [85.8–93.2]	55.9 [52.3–59.6]	93.5 [90.9–95.4]	44.1 [41.9–46.4]	0.18 [0.13–0.26]	2.04 [1.86–2.24]	28/278 (10.1)		
WBC ≥30 (µL)	92.5 [88.7–95.3]	51.5 [47.8–55.2]	94.6 [92.1–96.4]	42.4 [40.4–44.4]	0.15 [0.10–0.22]	1.91 [1.76–2.07]	21/278 (7.5)		
WBC ≥20 (µL)	94.9 [91.7–97.2]	45.0 [41.3–48.7]	95.9 [93.2–94.5]	40.0 [38.3–41.7]	0.11 [0.07–0.19]	1.73 [1.61–1.85]	14/278 (5.0)		
WBC ≥10 (µL)	97.8 [95.4–99.2]	34.9 [31.4–38.5]	97.7 [94.9–98.9]	36.7 [35.4–38.0]	0.06 [0.03]	1.50 [1.42–1.59]	6/278 (2.2)		

CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value; UFEME: urine full examination, microscopic examination; UTI: urinary tract infection; WBC: white blood cell

Table 5. Comparing different white blood cell threshold (nitrite negative) in culture-proven urinary tract infections. (Cont'd)

(B) In infants <1 year old (n=234).							
UFEME WBC threshold to diagnose UTI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	NPV (%) [95% CI]	PPV (%) [95% CI]	Negative Likelihood Ratio [95% CI]	Positive Likelihood Ratio [95% CI]	Number of missed UTI/ Total number of UTI (nitrite negative) (%)
WBC ≥100 (µL)	78.8 [70.1–85.9]	66.9 [57.8–75.2]	77.1 [69.8–83.1]	68.9 [62.9–74.5]	0.32 [0.22–0.46]	2.38 [1.82–3.12]	24/113 (21.2)
WBC ≥90 (µL)	79.7 [71.0–86.6]	66.1 [56.9–74.5]	77.7 [70.3–83.7]	68.7 [62.7–74.1]	0.31 [0.21–0.45]	2.35 [1.80–3.07]	23/113 (20.4)
WBC ≥80 (µL)	81.4 [73.1–88.1]	64.5 [55.3–72.9]	78.8 [71.2–84.8]	68.2 [62.4–73.4]	0.29 [0.19–0.43]	2.29 [1.77–2.96]	21/113 (18.6)
WBC ≥70 (µL)	82.3 [74.0–88.8]	60.3 [51.0–69.1]	78.5 [70.5–84.8]	65.9 [60.5–71.0]	0.29 [0.19–0.45]	2.07 [1.64–2.63]	20/113 (17.7)
WBC ≥60 (µL)	84.1 [76.0–90.3]	60.3 [51.0–69.1]	80.2 [72.2–86.4]	66.4 [61.0–71.4]	0.26 [0.17–0.41]	2.12 [1.68–2.68]	18/113 (15.9)
WBC ≥50 (µL)	84.9 [77.0–90.9]	59.5 [50.2–68.3]	80.9 [72.7–87.1]	66.2 [60.9–71.1]	0.25 [0.16–0.40]	2.10 [1.67–2.64]	17/113 (15.0)
WBC ≥40 (µL)	87.6 [80.1–93.1]	56.2 [48.9–65.2]	82.9 [74.4–89.1]	65.1 [60.1–69.8]	0.22 [0.13–0.37]	2.00 [1.62–2.48]	14/113 (12.4)
WBC ≥30 (µL)	90.3 [83.3–95.0]	52.9 [43.1–62.0]	85.3 [76.4–91.3]	64.2 [59.5–68.6]	0.18 [0.10–0.33]	1.92 [1.57–2.34]	11/113 (9.7)
WBC ≥20 (µL)	93.8 [87.7–97.5]	47.9 [38.8–57.2]	89.2 [79.8–94.6]	62.7 [58.5–66.8]	0.13 [0.06–0.27]	1.80 [1.51–2.15]	7/113 (6.2)
WBC ≥10 (µL)	96.5 [91.2–99.0]	42.2 [33.2–51.5]	92.7 [82.6–97.2]	60.9 [57.1–64.5]	0.08 [0.03–0.22]	1.67 [1.43–1.95]	4/113 (3.5)

CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value; UFEME: urine full examination, microscopic examination; UTI: urinary tract infection; WBC: white blood cell

as we would have missed 21.2% of UTI with a WBC threshold of $\geq 100/\mu\text{L}$, and this number would also be lowered to $<5\%$ with a WBC threshold of $\geq 10/\mu\text{L}$. Overall, a urinary WBC threshold of $\geq 10/\mu\text{L}$ would result annually in an estimated 419 extra urine specimens for urine culture with the same number started on empirical antibiotics.

We recognise that the decision on which WBC threshold to adopt should take into account both the number of missed UTIs as well as the additional resources required, including the number of urine cultures and patients started on empirical antibiotics. While a low WBC threshold will result in fewer missed UTI cases, there will also be a larger number of patients who are over-investigated and over-treated. After analysing the different WBC thresholds, a cross-disciplinary team in our hospital discussed and determined that lowering the WBC threshold to $\geq 50/\mu\text{L}$ would reduce the number of missed UTIs, while balancing an acceptable increase in the number of urine cultures being performed by the laboratory with a corresponding increase in number of patients started on empirical antibiotic treatment. By presenting the number of missed UTIs and corresponding increase in number of urine cultures at each urinary WBC threshold, our data serves to inform such decision-making in other outpatient contexts.

Of note, clinicians do not rely solely on the urinary WBC count in predicting UTI. Other parameters in the urinalysis which are useful in predicting UTI would be the presence of nitrite and micro-organisms. In addition to that, the patient's profile is also an important factor in predicting the likelihood of UTI. Infants have a higher rate of missed UTI compared to the overall paediatric population at all WBC thresholds, and WBC must be carefully reviewed together with patient's presentation as well as other urinary characteristics. In our study, boys appeared at higher risk of UTI, especially among infants, which is consistent with the literature.⁶ Other risk factors include urinary symptoms, vomiting, abdominal or flank pain, increase the likelihood of UTI by 2–6 fold.^{1,5} Therefore, for patients who have these symptoms, or infants who present with fever without any localising source, physicians should have a low threshold to suspect a UTI. In particular, among children with recurrent UTIs, especially in those who present with no other localising source of fever, physicians should send urine cultures and initiate empirical antibiotics as they have increased risk of kidney scarring.²⁰

The strength of this study is that it was carried out in a large children's ED. We were able to obtain urine samples from 1188 patients who had a wide range of urinary WBC values. We recognise the limitations of our study. We excluded febrile infants <3 months old because they are directly hospitalised with further investigations done as inpatient.

Future studies should include this population to understand the urinary characteristics and optimal urinary WBC threshold for UTI diagnosis, because they usually present with vague symptoms and largely have nitrite-negative urine samples.²¹ Based on clinical workflow, we only analysed urine samples that were screened positive via urine dipstick with a result of leukocyte esterase of 2+ and above. It is possible that we may have missed UTIs among those whose urine dipstick had $<2+$ leukocyte esterase. Our study did not allow us to directly compare the diagnostic performance of urinary dipstick leukocyte esterase and/or nitrite versus urinary microscopy WBC and/or nitrite in predicting UTI in the paediatric population. Also, among patients with insufficient urine samples for whom we were not able to submit urine for both urinalysis and urine culture, we may potentially have missed UTIs. In addition, urinalysis was performed on uncentrifuged urine. We did not take into account whether the concentration of urine may have affected the analysis of urine WBC. In future, analyses may be useful that look at urine concentration measured by way of osmolality in relation to the various urine WBC thresholds. Finally, this is a single-centre study, and validation in other centres is required to understand if our findings can be generalised.

CONCLUSION

We conclude that a urine microscopy WBC threshold of $100/\mu\text{L}$ results in a clinically significant number of missed UTIs. Adopting lower urinary WBC thresholds requires a value-judgement on overall resource utilisation including additional urine cultures and empirical antibiotics. It is also important for the clinicians to keep a high clinical index of suspicion for UTI if patients have risk factors for UTI.

Declaration

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

Ethics statement

This study was approved by the local ethics board with waiver of informed consent (Centralised Institutional Review Board CIRB 2023/2124, Singapore).

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