Association Between Uropathogen and Pyuria

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abstract

OBJECTIVE: We sought to determine factors associated with the absence of pyuria in symptomatic children whose urine culture was positive for a known uropathogen.

METHODS: We obtained data on children evaluated at the Children's Hospital of Pittsburgh emergency department between 2007 and 2013 with symptoms of urinary tract infection (UTI) who had paired urinalysis and urine cultures. We excluded children with an unknown or bag urine collection method, major genitourinary anomalies, immunocompromising conditions, or with multiple organisms on culture. We chose a single, randomly-selected urine specimen per child and limited the analysis to those with positive cultures.

RESULTS: There were 46 158 visits during the study period; 1181 children diagnosed with UTI met all inclusion criteria and had a microscopic urinalysis for pyuria. Pyuria (≥5 white blood cells per high-powered field or ≥10 white blood cells per cubic millimeter) was present in 1031 (87%) children and absent in 150 (13%). Children with *Enterococcus* species, *Klebsiella* species, and *Pseudomonas aeruginosa* were significantly less likely to exhibit pyuria than children with *Escherichia coli* (odds ratio of 0.14, 0.34, and 0.19, respectively). Children with these organisms were also less likely to have a positive leukocyte esterase on dipstick urinalysis. Results were similar when we restricted the analysis to children whose urine samples were collected by bladder catheterization.

CONCLUSIONS: We found that certain uropathogens are less likely to be associated with pyuria in symptomatic children. Identification of biomarkers more accurate than pyuria or leukocyte esterase may help reduce over- and undertreatment of UTIs.

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Dr Shaikh had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and participated in study concept and design and acquisition of data; Dr Shope participated in study concept and design analysis and interpretation of data; Ms Kurs-Lasky participated in analysis and interpretation of the data and statistical analysis; Drs Martin, Hoberman, and Vigliotti participated in analysis and interpretation of data; and all authors participated in drafting of the manuscript.

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WHAT'S KNOWN ON THIS SUBJECT: Approximately 10% of children with a positive urine culture and symptoms of a urinary tract infection lack pyuria on urinalysis. The reasons for this have not been systematically evaluated. Lack of pyuria could lead to delayed antimicrobial treatment.

WHAT THIS STUDY ADDS: We found that some uropathogens were less likely to be associated with pyuria. This suggests that urinalysis should always be accompanied by urine culture. Identification of bedside markers that are more accurate than pyuria could help improve patient outcomes.

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Clinicians rely heavily on the degree of pyuria (white blood cells [WBC] in the urine) when making a presumptive diagnosis of urinary tract infection (UTI). Lack of pyuria on an initial urinalysis may result in delayed diagnosis and delayed antimicrobial therapy. Accordingly, we sought to determine factors associated with the absence of pyuria in symptomatic children whose urine culture was positive for a known uropathogen.

We hypothesized, based on some preliminary data in adults,[1] that Gram-positive organisms (*Staphylococcus saprophiticus* and *Enterococcus* species) would cause less inflammation of the urinary tract and consequently cause less pyuria on urinalysis than infections caused by Gram-negative organisms (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella* species, *Proteus* species, and *Enterobacter* species), in which pyuria is observed in the vast majority of cases.[2,3]

METHODS

We obtained data on all children evaluated at the emergency department of Children's Hospital of Pittsburgh of UPMC between 2007 and 2013. We included only children <18 years of age with symptoms consistent with a diagnosis of UTI (Supplemental Table 3). We restricted eligible visits to those with a single urinalysis (UA) and a single urine culture, each obtained within 3 hours of the other. Children with known urinary tract abnormalities (eg, myelomeningocele, urinary stents) were excluded (see Supplemental Table 3). If a child had ≥1 eligible visit during the study period, a single episode of UTI was randomly selected. We then considered only children who had a positive urine culture (see below). Specimens obtained using a urine collection bag were excluded. We reviewed the electronic medical records of children included; those who were immunocompromised or taking immunosuppressive medications were excluded from all analyses. The study was approved by the University of Pittsburgh institutional review board.

Semiquantitative urine cultures were performed by using standard techniques. A positive urine culture was defined as growth of a single uropathogen at a concentration of ≥50 000 colony-forming units per milliliter from a catheterized specimen or a single uropathogen at a concentration of ≥100 000 colony-forming units per milliliter from a clean-voided specimen.

To determine the degree of pyuria, urine WBCs were counted either per high-powered microscopic field (hpf) or per cubic millimeter. The former was performed by using the IRIS urine chemistry analyzer (Iris Diagnostics, Chatsworth, CA), whereas the latter was performed manually by a laboratory technician using a hemocytometer. The type of test performed depended on the ordering physician's preference. No child had both tests performed. Pyuria was defined by the presence of a significant number of WBCs on microscopic urinalysis (≥5/hpf or ≥10/mm^3). A positive leukocyte esterase (LE) test on the urine dipstick was defined as 1+, 2+, or 3+ LE (0 or trace were considered negative). A total of 1181 children had a microscopic urinalysis for pyuria; of these, 1179 also had a LE test performed.

We used univariate logistic regression models to identify factors associated with the absence of pyuria and a positive LE test, respectively and calculated odds ratios (OR) and corresponding 95% two-sided confidence intervals (CI) accordingly.

RESULTS

Of the 1394 children <18 years of age with symptoms consistent with a diagnosis of UTI, paired UA and urine culture results, and a positive culture, 1181 (85%) met all inclusion criteria and had a microscopic urinalysis assessing for pyuria (Fig 1). In 694 (59%) children, urine was obtained by bladder catheterization. Table 1 describes demographic and clinical characteristics of the 1181 children. Overall, 89% were girls and 80% were white; median age was 23 months. Pyuria (≥5 WBC/hpf or ≥10 WBC/mm^3) was present in 1031 (87%) of children and absent in 150 (13%). Demographic characteristics were similar in children with and without pyuria. Of note, we found no difference between children <2 months of age and children ≥2 months of age regarding the proportions with pyuria (81.1% vs 87.9%, P = .09) or the proportions with a positive LE test (83.3% vs 88.8%, P = .17). The most frequently isolated organisms were *E coli*, *Klebsiella* species (41 *K pneumoniae*, 5 *K oxytoca*), *Enterococcus* species (34 *E faecalis,* 1 other*)*, *Proteus* species (29 *P mirabilis*, 2 other), and *Enterobacter* species (13 *E cloacae*, 2 other) representing 85%, 4%, 3%, 3%, and 1% of positive urine cultures, respectively.

Children whose urine culture yielded organisms other than *E coli* were significantly less likely to have pyuria (OR and 95% CI: 0.39 [0.26–0.58], P < .001) or a positive LE test (OR and 95% CI: 0.27 [0.18–0.41], P < .001 when compared with those whose urine culture yielded *E coli*. Specifically, children with *P aeruginosa*, *Enterococcus* species, or *Klebsiella* species were significantly less likely to have pyuria than children with *E coli* (OR and 95% CI: 0.19 [0.06–0.60], P = .004; 0.14 [0.07–0.28], P < .001; 0.34 [0.17–0.68], P = .002, respectively) (Table 2). Results were similar for the LE test (Table 2).

Results were also similar when we restricted analysis to children whose urine specimen was

obtained by bladder catheterization (Supplemental Table 4). Children with *Enterococcus* or *Klebsiella* species were significantly less likely to have pyuria than children with *E. coli* (OR and 95% CI: 0.14 [0.05–0.38], $P < .001$; 0.37 [0.17– 0.80], $P = .01$, respectively) (Supplemental Table 4). Results for children with *P aeruginosa* differed from the main analysis; however, this finding may be related to a relatively small number of children ($n = 7$). Results were similar for the LE test.

DISCUSSION

We found that in children with apparent UTI, the proportion with pyuria varied significantly according to the uropathogen present. Compared with *E coli*, the odds of pyuria were 3 to 5 times lower with certain organisms (*Enterococcus* and *Klebsiella* species and *P aeruginosa*). Contrary to what we had hypothesized, however, Gram-stained smear characteristics of the uropathogen were not a good predictor of the odds of pyuria. Rather, within Gram-stained smear groups, there were differences among species.

The most recent American Academy of Pediatrics guideline suggests that pyuria should be present when diagnosing a UTI.[4] The rationale for this recommendation is to prevent children whose urine culture may be contaminated as a result of poor collection technique (bag-collected urine specimen), or children with asymptomatic bacteriuria, from being diagnosed as having a UTI and receiving unnecessary antimicrobial agents. However, only 90%[5] of children with UTI exhibit pyuria even when the urine specimen is collected by bladder catheterization or suprapubic aspiration. Furthermore, the prevalence of asymptomatic bacteriuria is too low (<1%)[6] to fully explain why many children with an apparent UTI lack pyuria. Findings

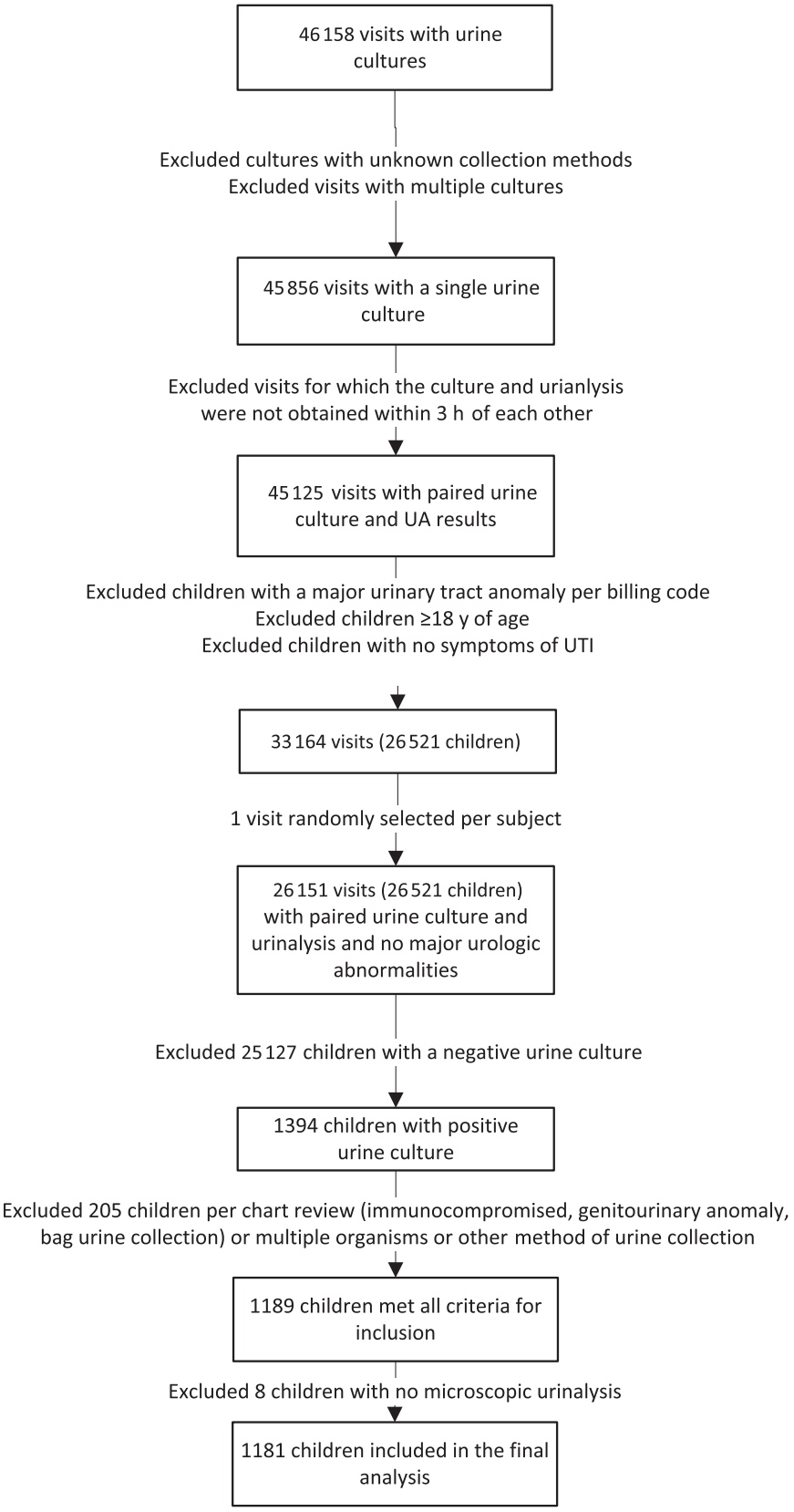

FIGURE 1
Flow of children in the study.

TABLE 1 Demographic and Clinical Characteristics of the 1181 Children With a Positive Urine Culture According to the Presence of Pyuria

Characteristic	Pyuria[a], *N* = 1031	No Pyuria, *N* = 150	*P*[b]
Age (%)			.06
<2 mo	73 (81.1)	17 (18.9)	
2–11 mo	321 (87.0)	48 (13.0)	
12–23 mo	114 (83.8)	22 (16.2)	
2–5 y	242 (87.1)	36 (12.9)	
6–17 y	281 (91.2)	27 (8.8)	
Gender (%)			.35
Boy	120 (90.2)	13 (9.8)	
Girl	910 (86.9)	137 (13.1)	
Missing	1	0	
Race (%)			.93
White	811 (87.0)	121 (13.0)	
African American	165 (87.8)	23 (12.2)	
Other	30 (85.7)	5 (14.3)	
Missing	22	1	
Temperature (%)			.78
<39°C	666 (87.5)	95 (12.5)	
≥39°C	354 (86.8)	54 (13.2)	
Missing	11	1	

[a] Pyuria = ≥5 WBC/hpf or ≥10 WBC/mL^3.
[b] Proportions were compared by using a χ^2 test.

TABLE 2 Presence of Pyuria or LE in Urine Samples of 1181 Children With UTI According to Uropathogen

Pathogen	Diagnostic Test	
	Pyuria[a], % (No.)	LE ≥1, % (No.)
E. coli	89.3 (892/999)	91.1 (908/997)
P. aeruginosa	61.5[b] (8/13)	61.5[b] (8/13)
S. saprophiticus	100 (27/27)	96.3 (26/27)
Enterococcus species	54.3[b] (19/35)	48.6[b] (17/35)
Klebsiella species	73.9[b] (34/46)	71.7[b] (33/46)
Proteus species	80.6 (25/31)	83.9 (26/31)
Enterobacter species	86.7 (13/15)	80.0 (12/15)
Other	86.7 (13/15)	80.0 (12/15)

[a] Pyuria = ≥5 WBC/hpf or ≥10 WBC/mL^3.
[b] Significantly different from *E. coli* at α = 0.01.

of our study offer an additional explanation for the absence of pyuria: some uropathogens may not elicit a strong host inflammatory response. Accordingly, our findings suggest that bedside biomarkers that are more sensitive and specific than pyuria are needed to improve the accuracy of early diagnosis.

Multiple reasons could explain differences in the occurrence of pyuria in children diagnosed with UTI with different uropathogens. Some uropathogens form biofilms, which could affect the host's ability to mount an inflammatory response.[7] Other uropathogens (*E coli*, *Klebsiella* species, and *Enterococcus* species) form intracellular bacterial communities, which may also affect the immune response.[7] Other yet-to-be-determined genetic or anatomic factors linked to susceptibility to certain pathogens may also be related to the host's immune response.

We found that children with certain non–*E coli* organisms had lower odds of exhibiting pyuria than children with *E coli*. Absence of pyuria can lead to a delay in diagnosis and treatment of UTIs. A delay in treatment has been associated with a higher likelihood of renal scarring.[8–11] This may partly explain why, in a recent meta-analysis, children with UTIs caused by non-*E coli* organisms were more likely to develop renal scarring.[12]

Our results suggest that pyuria may not always be present in children with UTIs, especially those caused by *Enterococcus* species, *Klebsiella* species, or *P aeruginosa*. Accordingly, in acutely ill children suspected of having a UTI, empirical therapy while awaiting culture results may represent a reasonable approach if there are indications (see below) that organisms other than *E coli* may be involved. The presence of nitrites is highly specific for UTI caused by bacteria in the Enterobacteriaceae family (*E coli*, *Klebsiella* species, and *Proteus* species). Therefore, a child in whom the clinical suspicion is high who presents with a positive nitrite test on the dipstick UA but no pyuria may have a UTI caused by *E coli* or *Klebsiella* and could be treated empirically. Similarly, a child with Gram-positive cocci on a Gram stain smear who presents without pyuria may have an *Enterococcal* UTI. Our results also suggest that in children suspected of having UTI on clinical grounds, both a urinalysis and a urine culture should be performed.

Limitations of our study include use of a database to identify a large sample retrospectively. Although we depended on accurate coding for entry into the study, we conducted a chart review to ascertain that included children did not meet any of our exclusion criteria. Some children in this study may not have had a true UTI; as previously mentioned, a positive urine culture in the absence of pyuria may result from asymptomatic bacteriuria or contaminated specimens. However, because we excluded bag-collected specimens, we expect this proportion to be relatively low.[6] Furthermore, our results did not vary by urine specimen collection method. In addition, we only included children who presented with symptoms consistent with UTI and used

stringent criteria to define a positive urine culture. Accordingly, it is likely that a large portion of children with no pyuria who were included had true UTIs. Finally, neither asymptomatic bacteriuria nor contamination explain the marked differences we found in the occurrence of pyuria among uropathogens.

This study suggests that pyuria may be absent in some children with certain uropathogens. Accordingly, urine cultures should be performed in all children clinically suspected of having a UTI. New point-of-care tests that are more sensitive and specific than pyuria could help reduce over- and undertreatment of this frequently occurring pediatric problem.

ABBREVIATIONS

CI: confidence interval
hpf: high-powered microscopic field
LE: leukocyte esterase
OR: odds ratio
UA: Urinalysis
UTI: urinary tract infection
WBC: white blood cell

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