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Can a Simple Urinalysis Predict the Causative Agent and the Antibiotic Sensitivities?

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Abstract

Objectives—The objective of this study was (1) to determine the reliability of urinalysis (UA) for predicting urinary tract infection (UTI) in febrile children, (2) to determine whether UA findings can predict *Escherichia coli* versus non-*E. coli* urinary tract infection, and (3) to determine if empiric antibiotics should be selected based on *E. coli* versus non-*E. coli* infection predictions.

Methods—This was a retrospective chart review of children from 2 months to 2 years of age who presented to the emergency department with fever (rectal temperature >100.4°F) and had a positive urine culture. This study was conducted between January 2004 and December 2007. Negative UA was defined as urine white blood cell count less than 5 per high-power field, negative leukocyte esterase, and negative nitrites. Urine cultures were classified into *E. coli* and non-*E. coli* groups. These groups were compared for sex, race, and UA findings. Multivariate forward logistic regression, using the Wald test, was performed to calculate the likelihood ratio (LR) of each variable (eg, sex, race, UA parameters) in predicting UTI. In addition, antibiotic sensitivities between both groups were compared.

Results—Of 749 medical records reviewed, 608 were included; negative UA(–) was present in 183 cases, and positive UA(+) was observed in 425 cases. Furthermore, 424 cases were caused by *E. coli*, and 184 were due to non-*E. coli* organisms. Among 425 UA(+) cases, *E. coli* was identified in 349 (82.1%), whereas non-*E. coli* organisms were present in 76 (17.9%); in contrast, in 183 UA(–) cases, 108 (59%) were due to non-*E. coli* organisms versus 75 (41%), which were caused by *E. coli*. Urinalysis results were shown to be associated with organism group ($P < 0.001$). Positive leukocytes esterase had an LR of 2.5 (95% confidence interval [CI], 1.5–4.2), positive nitrites had an LR of 2.8 (95% CI, 1.4–5.5), and urine white blood cell count had an LR of 1.8 (95% CI, 1.3–2.4) in predicting *E. coli* versus non-*E. coli* infections. Antibiotic sensitivity compared between UA groups demonstrated equivalent superiority of cefazolin (94.7% sensitive in UA(+) vs 84.0% in UA(–) group; $P < 0.0001$), cefuroxime (98.2% vs 91.7%; $P < 0.001$), and

nitrofurantoin (96.1% vs 82.2%; $P < 0.0001$) in the UA(+) group. In contrast, the UA(−) group showed significant sensitivity to trimethoprim-sulfamethoxazole (82.2% vs 71.3% in UA(+); $P = 0.008$).

Conclusions—Urinalysis is not an accurate predictor of UTI. A positive urine culture in the presence of negative UA most likely grew non-*E. coli* organisms, whereas most UA(+) results were associated with *E. coli*. This study also highlighted local patterns of antibiotic resistance between *E. coli* and non-*E. coli* groups. Negative UA results in the presence of strong suspicion of a UTI suggest a non-*E. coli* organism, which may be best treated with trimethoprim-sulfamethoxazole. Conversely, UA(+) results suggest *E. coli*, which calls for treatment with cefazolin or cefuroxime.

Keywords

urinary tract infection; fever; urinalysis; antibiotic sensitivity

Urinary tract infection (UTI) is a common cause of serious bacterial infection in young febrile children. Urinary tract infections in children make up for up to 14% of pediatric emergency department (ED) visits in the United States annually.¹ This accounts for more than 70,000 children in the United States developing UTIs each year.² In a meta-analysis, pooled prevalence of UTIs among febrile children younger than 24 months was 7%.³ Other studies have reported a 5% prevalence of UTI in febrile infants without a source.^{4,5} The American Academy of Pediatrics UTI clinical practice guideline recommends that UTI should be highly suspected in febrile children between the ages of 2 months and 2 years.⁶ Febrile UTIs have the highest incidence during the first year of life in both sexes.⁷

The diagnosis of UTI can be difficult because of nonspecific signs and symptoms as well as the challenges of obtaining an accurate history and physical examination in young children. Urine culture (UC) is the criterion standard for diagnosing UTI.³ Most physicians are in agreement that in a young febrile child a proper UC should be obtained either by suprapubic aspiration or by bladder catheterization.⁸

However, UC results are not readily available in the ED. Therefore, decisions in the ED are often based on the initial urinalysis (UA) findings. We have noted, on occasion, that UTIs may be confirmed by UC even when the UA result is negative. Studies have shown that as many as 10% to 50% of patients with UTIs documented by positive UC can have a negative UA.^{9–12}

Although the most common organism causing UTIs in children is *Escherichia coli*, accounting for up to 70% of infections,¹³ up to one third of UTIs are caused by non-*E. coli* organisms.¹ The relative prevalence of non-*E. coli* UTIs has been reported to be rising from 25% to 40% in the present study.¹⁴ Non-*E. coli* UTI also been reported to be associated with higher antimicrobial resistance and a higher rate of inappropriate empiric antibiotic therapy.¹⁴ This study has also demonstrated a 10-fold higher rate of inappropriate initial antibiotic therapy administered for non-*E. coli* UTI than *E. coli* UTI.¹⁴

If not detected and treated promptly, UTI can result in sequelae such as renal scarring, hypertension, and end-stage renal disease.¹³ Urinary tract infections in children younger than 2 years have been associated with significant morbidity and long-term medical consequences.¹⁵ Because outcome depends on a timely diagnosis and appropriate selection of antibiotic treatment, accurate detection of organism is important.

MATERIALS AND METHODS

This is a retrospective review of febrile children who presented to the ED and in whom UA and UC were obtained. Only children with a positive UC results were included. This study was conducted between January 2004 and December 2007. This study received approval from the institutional review board of the hospital. The following information was collected from the medical record by 2 trained research assistants: demographic information (age, race, sex), UA findings (urine white blood cell [WBC], leukocyte esterase [LE], and nitrite), and antibiotic sensitivity results. Exclusion criteria included cases with polymicrobial infection, incomplete UA information on white blood cell count, LE, and nitrite, in addition to incomplete antibiotic sensitivity results. A standardized data collection form was prepared and utilized for data collection.

All urine specimens were obtained by sterile urethral catheterization. Urinalysis and UC were obtained simultaneously. All specimens were transported to a common laboratory in the Uricult container (Cardinal Health, Dublin, Ohio). Negative UA was defined as urine WBC count of less than 5 per high-power field (HPF), negative LE, and negative nitrites status. Conversely, positive UC was defined as the presence of pure colonies of 10,000 colony-forming units or more. Urinary tract infections were classified into *E. coli* and non-*E. coli* groups based on UC results. The 2 groups were compared for UA findings (LE and nitrite status) and culture organism. A χ^2 test was performed for statistical analysis. Multivariate forward logistic regression, using the Wald test, was performed to calculate the likelihood ratio (LR) of each variable (eg, sex, race, UA parameters) in predicting UTI.

RESULTS

Over the study period, 749 children with positive UC were identified. We excluded 141 children because of incomplete UA results, antibiotic sensitivity data, and polymicrobial infection. Among 608 children with culture-proven UTI, 425 cases (69.9%) had positive UAs, and 183 (30.1%) had negative UAs (Fig. 1). Among 425 patients with positive UA, 349 (82.1%) were due to *E. coli*, and 76 (17.9%) were caused by non-*E. coli* organisms. Of the 183 patients with negative UA, 75 (41.0%) were due to *E. coli*, and 108 (59.0%) were caused by non-*E. coli* bacteria. Overall, among 608 children, 424 (69.7%) cases were caused by *E. coli*, and 184 (30.3%) were due to non-*E. coli* organisms.

With respect to sex, UA was positive in 211 males (49.6%) and 214 females (50.4%). Urinalysis was negative in 132 males (72.1%) and 51 females (27.9%). Furthermore, males and females were equally affected in 424 *E. coli* cases (213 [50.2%] vs 211 [49.8%], respectively). In 184 non-*E. coli* cases, 130 (70.7%) were male, and 54 (29.3%) were female. Regarding overall sex distribution of UTI cases, 343 were male, of which 213

(62.1%) were due to *E. coli* and 130 (37.9%) caused by non-*E. coli*. In 265 females with UTI, 211 cases (79.6%) were due to *E. coli*, and 54 (20.4%) were caused by non-*E. coli* (odds ratio [OR], 2.4; 95% confidence interval [CI], 1.6–3.5). Regarding race, 506 patients were Hispanic, 65 were African American, and 37 were classified as other. Among these races, *E. coli* was the major uropathogen implicated in more than 50% of cases. The demographic distribution regarding sex and race is summarized in Table 1.

Among UA parameters (Table 2), positive LE was present in 386 cases (63.5%) and negative in 222 cases (36.5%). Furthermore, 325 LE(+) cases (84.2%) were due to *E. coli*, whereas 61 (15.8%) were due to non-*E. coli* organisms. In 222 LE(–) cases, 99 (44.6%) were *E. coli*, and 123 (55.4%) were caused by non-*E. coli*. Positive LE status was more often observed in *E. coli* UTI (OR, 6.6; 95% CI, 4.5–9.7) than in non-*E. coli* UTI. In addition, nitrites were positive in 127 cases (20.9%) and negative in 481 cases (79.1%). Among 127 nitrite positive cases, 116 (91.3%) were caused by *E. coli*, and 11 (8.7%) were due to non-*E. coli* organisms. In 481 nitrite-negative cases, 308 (64.0%) were caused by *E. coli*, and 173 (36.0%) were non-*E. coli*. Overall, positive nitrites were more likely to be predictive of *E. coli* UTI (OR, 5.9; 95% CI, 3.1–11.3).

Multivariate forward logistic regression using the Wald test was performed to assess the LRs of the variables discussed above. Positive leukocytes esterase had an LR of 2.5 (95% CI, 1.5–4.2), positive nitrites had an LR of 2.8 (95% CI, 1.4–5.5), and urine WBC count had an LR of 1.8 (95% CI, 1.3–2.4) in predicting *E. coli* versus non-*E. coli* infections. Indeed, positive UA was highly predictive of *E. coli* UTIs. Furthermore, male sex carried a higher likelihood for non-*E. coli* infections. Male sex is a borderline negative risk factor for *E. coli* infections with an LR of 1.6 (95% CI, 1.1–2.4). In contrast, race had no predictive value ($P > 0.05$). Hispanic race had an LR of 1.6 (95% CI, 0.7–3.5), whereas African American race carried an LR of 1.5 (95% CI, 0.6–4.0).

A review of antibiotic sensitivity patterns between UTI groups (Table 3) demonstrated the superiority of cefazolin and cefuroxime in both UA(+) and *E. coli* UTIs. Cefazolin sensitivity was observed in 372 (94.7%) and 386 (97.0%) of UA(+) and *E. coli* cases, respectively ($P < 0.0001$). For cefuroxime, sensitivity was shown in 377 (98.2%) and 382 (99.0%) of UA(+) and *E. coli* cases, respectively ($P < 0.0001$). Both agents were shown to have only less than 92% sensitivity among UA(–) and non-*E. coli* groups ($P < 0.001$). Furthermore, trimethoprim-sulfamethoxazole demonstrated effectiveness in 125 (82.2%; $P = 0.008$) and 129 (88.4%; $P < 0.0001$) cases in UA(–) and non-*E. coli* groups, respectively. Furthermore, trimethoprim-sulfamethoxazole sensitivity was observed in only 288 (71.3%) and 284 (69.3%) of UA(+) and *E. coli* cases, respectively.

DISCUSSION

Urine culture is the criterion standard and is the test required for the diagnosis of UTI. However, results of UC are not readily available in the ED. We conducted this study to determine the utility of UA and also to determine whether the organism in the UC can be predicted based on the initial UA results in febrile children between the ages of 2 and 24 months. Furthermore, identification of uropathogenic organisms was carried out to elucidate

possible distinguishing characteristics between non-*E. coli* and *E. coli* UTI with respect to these parameters, as well as variation in local resistance patterns.

Conceivably, empirical treatment of pediatric UTIs can be better guided by establishing such potential relationships. Studies have identified 5 risk factors predicting the likelihood of UTI in children: white race, age younger than 12 months, temperature 39°C or greater, fever for 2 or more days, and absence of another source of infection. This prediction rule has a sensitivity of 88% but a specificity of 33%.^{16–18} Therefore, there remains a need for a better diagnostic approach in the management of febrile children.

In this study, UA was negative in 30% of children with positive UC. This is in agreement with previous studies, which have demonstrated poor concordance between UA and UC results. Between 10% and 50% of patients with positive UC may have an initial negative UA result.^{10,11} Another study reported 96% negative predictive value of UA (95% CI, 93%–97%) in predicting positive UC, but sensitivity was 64% (95% CI, 49%–78%) and specificity was 91% (95% CI, 88%–94%).¹⁹ This negative predictive value, with low sensitivity, may be related to the low prevalence of positive UCs. It is important to recognize that despite a negative UA, UTI still cannot be excluded with certainty.

Generally, presence of at least 50,000 colony-forming units per milliliter from a catheterized specimen is considered significant.²⁰ Furthermore, the presence of at least 10 WBCs/mL from an unspun specimen examined using a counting chamber or at least 5 WBCs/HPF from a centrifuged specimen constitute significant pyuria.²¹ For this study, we considered UA as negative if urine WBCs less than 5/HPF, urine LE, and nitrites were all negative. If any one of those were positive, the UA was categorized as positive. Of note, urinary nitrite, however, is not a sensitive marker for UTI in children, particularly infants, because of their frequent bladder emptying.⁶ In addition, many uropathogens do not reduce nitrate to nitrite.⁶ Our study predictably showed that almost one third of children with positive UC had negative UA. Because missed diagnoses of UTI, if untreated, can lead to significant sequelae, this finding has an important clinical implication.

Identifying factors in the initial UA that can potentially predict an *E. coli* versus non-*E. coli* UTI can be important to direct empirical antibiotic therapy. Previous studies have reported that *E. coli* usually causes 65% to 90% of all urinary infections in children.^{22–24} In another study, up to one third of UTIs were caused by non-*E. coli* organisms.¹ In our study, up to 30% of all culture-proven UTIs were due to non-*E. coli* organisms.

It has been reported that patients with non-*E. coli* UTI were younger and had milder clinical signs, longer hospitalization, and higher rate of urinary tract anomalies.¹ In another study, higher rate of antimicrobial resistance and inappropriate empiric antibiotic therapy was reported in non-*E. coli* UTI.¹⁴ Three significant independent risk factors for non-*E. coli* UTI have been described: (1) previous antimicrobial therapy, (2) male sex, and (3) underlying renal abnormalities. Our study showed higher association of negative UA with non-*E. coli* UTI regardless of sex. In addition, UA positivity was significantly associated with *E. coli* UTI, and this association was stronger in females ($P < 0.001$).

We analyzed the resistance of the organism isolated in the UC to antimicrobial agents usually recommended for empiric treatment of UTI in children. Trimethoprim-sulfamethoxazole had a superior sensitivity in non-*E. coli* UA-negative group and cefazolin or cefuroxime were more appropriate for *E. coli*/UA-positive children. The benefits of trimethoprim-sulfamethoxazole in preventing long-term sequelae of pediatric UTI must be weighed against its adverse effect profile such as Stevens-Johnson syndrome and blood dyscrasias.

This study provided valuable information regarding UTI in an ethnic minority population. Clinical Practice Guideline for the Diagnosis and Management of Initial UTI in Febrile Infants and Children 2 to 24 months states that data regarding UTI rates in Hispanic individuals are limited.⁶ In our study, all urine specimens were obtained by catheterization, which minimized the risk of sample contamination.

LIMITATIONS

One of the limitations of our study was the inability to categorize male children based on their circumcision status in light of the preponderance of UTI in uncircumcised boys.^{25,26} Previous studies have demonstrated that circumcision status is the greatest risk factor in males at risk of UTIs.³ Uncircumcised male infants are about 10 times more likely to develop UTIs than circumcised infants.²⁷ Circumcision has been reported to prevent recurrent symptomatic UTIs.²⁸ The medical records that we reviewed did not have consistent reporting of circumcision status of children. A 2012 survey by Bisono et al²⁹ taken in Washington Heights/Inwood, a nearby Hispanic community, estimates the rate of circumcision to be 33%. Whether our population has a similar circumcision rate is questionable because of differing cultural and racial composition as well as immigration patterns. As such, circumcision rate was not taken into consideration in our study.

Another limitation of our study is the absence of information regarding antibiotic pretreatment. Antibiotic pretreatment preferentially selects certain organisms in the gut flora that can potentially influence the probability of acquiring an *E. coli* rather than a non-*E. coli* UTI. Furthermore, regionality of antibiotic sensitivity precludes our findings from being applied in areas outside the South Bronx.

Our retrospective study was conducted in a hospital serving a community mostly populated by Hispanics. Therefore, investigating the distribution of prevalence of UTI among different races was limited, especially among whites. The racial distribution between *E. coli* and non-*E. coli* UTI was similar. In addition, our study demonstrated higher proportion of males (almost 56%) as opposed to 27% males in a previous study.¹⁹ This may be related to the difference in circumcision practice among study populations.

CONCLUSIONS

A negative UA does not reliably predict a negative UC. A negative UA is most likely associated with non-*E. coli* organisms, whereas most of positive UAs were associated with *E. coli*. Trimethoprim-sulfamethoxazole had a superior sensitivity in non-*E. coli* UA-

negative group, and cefazolin or cefuroxime was more appropriate for the *E. coli*/UA-positive group.

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FIGURE 1.
Overall urinalysis and urine culture results.

TABLE 1

Demographic Distribution Between UTI Groups

	<i>E. coli</i> UTI	Non- <i>E. coli</i> UTI
Sex		
Male	213 (62.1%)	130 (37.9%)
Female	211 (79.6%)	54 (20.4%)
Race		
Hispanic	359 (70.9%)	147 (29.1%)
Black	44 (67.7%)	21 (32.3%)
Others	21 (56.8%)	16 (43.2%)

TABLE 2

UA Parameters (LE and Nitrite Status) Among UTI Groups

	<i>E. coli</i> UTI	Non- <i>E. coli</i> UTI	LR (95% CI)
LE			
LE(+)	325 (84.2%)	61 (15.8%)	2.5 (1.5–4.2)
LE(–)	99 (44.6%)	123 (55.4%)	
Nitrite			
Nitrite(+)	116 (91.3%)	11 (8.7%)	2.8 (1.4–5.5)
Nitrite(–)	308 (64.0%)	173 (36.0%)	

TABLE 3

Antibiotic Sensitivity Among UTI Groups and UA Result Groups

Antibiotic	<i>E. coli</i>	Non- <i>E. coli</i>	<i>P</i>	UA(+)	UA(-)	<i>P</i>
Cefazolin	97.0%	77.2%	<0.0001	94.7%	84.0%	<0.0001
Cefuroxime	99.0%	89.3%	<0.0001	98.2%	91.7%	<0.001
Trimethoprim-sulfamethoxazole	69.3%	88.4%	<0.0001	71.3%	82.2%	0.008