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Evaluation of BacterioScan 216Dx in Comparison to Urinalysis as a Screening Tool for Diagnosis of Urinary Tract Infections in Children

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ABSTRACT Urinalysis (UA) has routinely been used as a screening tool prior to urine culture set up. BacterioScan 216Dx is an FDA-cleared semiautomated system to detect bacterial growth in urine. The aim of this study was to evaluate 216Dx in comparison to UA for diagnosis of urinary tract infection (UTI) in children. Clean-catch, unpreserved urine samples from children aged <18 years were tested by 216Dx, and positive urine samples in media were processed for direct bacterial identification by matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry. Sensitivity and specificity of 216Dx and urinalysis (UA) were determined against urine culture. Of 287 urine samples obtained from children (median age, 108 months), 44.0% and 56.0% were UA positive and negative, respectively, while 216Dx detected 27% and 73% as positive and negative, respectively. Compared to culture, the overall sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 216Dx versus UA were 92.1% versus 97.3%, 82.7% versus 63.8%, 44.8% versus 29.1%, and 98.6% versus 99.3%, respectively. Among 216Dx true-positive (TP) samples ($n = 35$), 77.0% were successfully identified directly from broth by MALDI-TOF. Among urine samples that were identified as contaminated by culture ($n = 127$; 44%), the 216Dx detected 93 (73.0%) as negative while UA detected 69 (54.0%) as negative. Although the sensitivities of 216Dx and UA are comparable, the specificity of 216Dx was higher than that of UA. The 216Dx can be used as an alternative/adjunct screening tool to UA to rule out urinary tract infection (UTI) in children. Compared to culture, the faster turnaround time (3 hours) of 216Dx has the potential to reduce unnecessary antibiotic use and improve patient management.

KEYWORDS BacterioScanTM 216Dx, urinalysis, urine culture, children, contamination, rapid diagnosis

Urinary tract infection (UTI) is one of the most common infections in the United States, resulting in 8.6 million health care visits, 1 million emergency department visits, and 100,000 hospitalizations per year, with a total economic burden of nearly $2 billion (1, 2). In the pediatric population, UTI is the most common serious bacterial infection in febrile infants requiring antibiotic prescriptions (3, 4). Urine culture is one of the most frequently ordered clinical laboratory tests and usually occupies two-thirds of all culture work-up (5), and yet, the majority of the specimen results are negative or contaminated by the plate-based culture method, which remains the gold standard. The plate-based culture method usually takes 24 to 48 hours for initial identification, a time delay that compels clinicians to prescribe empirical antibiotics (6, 7). A recent retrospective study of patients aged ≤21 years reported that almost half of the patients

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discharged home with antibiotic prescription were later found to be culture negative for UTI (6).

Urinalysis (UA) has been used as a screening test for the presumptive diagnosis of UTI due to its short turnaround time of less than 1 hour. Typically, UA results of either nitrite positive, leukocyte esterase of ≥trace, or white blood cell counts between 5 and 10 per high power field (hpf) are considered indicative of bacterial infection of the urinary tract (8–11). However, the sensitivity and specificity of UA are often variable in children, ranging from 64.0% to 94.0% (12, 13).

BacterioScan 216Dx is a recently FDA-cleared semiautomated system for qualitative determination of the presence or absence of viable bacteria in urine samples (14). This instrument analyzes light-scattering profiles to assess bacterial growth directly from urine samples incubated in liquid media, and results are available in 3 hours. To our knowledge, no data are available on the direct head-to-head comparison between urinalysis and the 216Dx system for the detection of UTI in the pediatric population. The aim of this study was to compare the performance of 216Dx and UA as screening tools for the diagnosis of UTI in children.

MATERIALS AND METHODS

Sample collection. Nonpreserved, midstream clean-catch, leftover urine samples obtained from children <18 years of age were included in this study and collected between March and April 2018. Bloody or visibly turbid samples were excluded. All urine samples were stored and transported in refrigerated condition and were tested by 216Dx and set-up for culture within 24 hours of collection. This study was reviewed and approved by the Institutional Review Board at Children's Mercy Hospital.

Urinalysis. Urinalysis was done using the automated iRICELL3000 analyzer (Beckman Coulter, CA). Urine samples were considered UA positive if they met any of the following criteria: (i) leukocyte esterase of ≥trace, (ii) nitrite positive, or (iii) count of white blood cells of ≥5/hpf. UA-positive samples were reflexed to bacterial culture. For the purpose of the study, UA-negative samples were collected and culture was set up in the Children's Mercy clinical microbiology laboratory according to laboratory standard operating procedure (SOP) following 216Dx testing.

BacterioScan 216Dx testing. All urine testing was done according to the manufacturer's instructions. In brief, 2.5 ml of tryptic soy broth (TSB) was dispensed to each multicuvette by manual pipetting. Next, 360 μl of each urine specimen was individually dispensed to multicuvette slots and mixed by manual pipetting up and down 4 to 5 times. After closure of the lids, sample information was entered into the 216Dx graphical user interface (GUI). Following a 3-hour incubation and evaluation of all loaded samples, the GUI returned a qualitative "presumptive positive/presumptive negative" result.

Pathogen identification by matrix-assisted laser desorption ionization–time of flight mass spectrometry. All samples flagged as presumptive positive by 216Dx were further evaluated by matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry for identification. A total of 1.5 ml of positive samples was transferred from the multicuvette into a 2.0-ml tube and centrifuged for 5 min at 16,000 × *g* (Eppendorf, NY). Supernatant was carefully removed, and using a sterile toothpick, a small amount of pellet was transferred to sample plate for direct MALDI-TOF identification (Bruker Daltonics, MA). The standard Bruker MALDI-TOF mass spectrometry (MS) protocol, including application of matrix and bacterial test standard controls, was followed. The target was then run on the clinical application program of the MALDI-TOF MS instrument. Results were interpreted according to the manufacturer's specifications (expanded claim 3).

Bacterial plate-based culture method. Bacterial culture was used as a reference standard. All samples underwent bacterial culture according to laboratory SOP. In brief, a 0.001-ml loop was used to culture bacteria on a blood and MacConkey agar plate (Thermo Scientific Remel, KS) that was incubated at 35°C for up to 48 hours. Per our laboratory protocol, for clean-catch urine samples, a positive culture was defined as growth of any known single uropathogen at ≥10,000 CFU/ml. If two organisms were isolated on a plate, the cutoff for work-up of both bacteria was >100,000 CFU/ml for each organism or a single uropathogen of >10,000 CFU/ml isolated at 10 times excess colony count than the second organism. Any cultures with growth that did not meet the colony count criteria or had ≥3 types of organisms were grouped as contaminants (15). Negative urine culture was defined as no growth.

Statistical analysis. Culture-positive and -negative groups were compared across various demographic and sample variables using chi-square, Fisher's exact, and Wilcoxon signed-rank tests. Statistical analysis on the difference in diagnostic yield among the assays was analyzed using McNemar's and Fisher's exact tests. Reportable data were summarized in two-by-two data tables listing the number of specimens in each of the four result categories, namely, true positive (TP), true negative (TN), false positive (FP), and false negative (FN). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated against bacterial culture and MALDI-TOF MS identification. For the purpose of this analysis, all contaminated urine samples identified by reference standard were categorized as negative.

TABLE 1 Patient demographics and sample characteristics[a]

Patient characteristic	Overall values[b] (n = 287)	Values[c] by culture result		P value
		Pos (n = 38)	Neg[d] (n = 249)	
Female	217	36 (17.0)	181 (83.0)	0.003
Male	70	2 (3.0)	68 (97.0)	
Age in months (IQR)	108 (90–156)	84 (60–180)	108 (60–156)	0.677
ED	93	6 (6.0)	87 (94.0)	<0.001
IP	56	1 (0.5)	55 (99.5)	
OP	71	12 (17.0)	59 (83.0)	
UC	67	19 (28.0)	48 (72.0)	
UA results				
Esterase ≥trace	120	35 (29.0)	85 (71.0)	<0.001
Nitrite pos	9	9 (100.0)	0	<0.001
WBC (≥5/hpf)	89	31 (35.0)	58 (65.0)	<0.001

[a]ED, emergency department; IP, in patient; OP, out-patient clinic; UC, urgent care; hpf, high power field; pos, positive; neg, negative; IQR, interquartile range.
[b]Values are n except where indicated.
[c]Values are n (%) except where indicated.
[d]Included no growth, contamination.

RESULTS

A total of 287 leftover urine samples were included in this study. The overall urine culture positivity rate was 13.0% (38/287), the rate of contamination was 44.0% (127/287), and no growth was observed in 42.5% (122/287) cases. Among these cases, 44% (127/287) and 23% (78/287) were positive by UA and 216Dx, respectively. Brief patient demographic and sample characteristics are provided in Table 1. The majority (28.0%) of the culture-positive samples came from urgent care, followed by the outpatient clinics (17.0%).

The overall diagnostic accuracy was higher for 216Dx (84.0%) than UA (68.0%) ($P <$ 0.0001) with urine culture as the reference method. The sensitivity of UA was comparable to the 216Dx system (97.3% versus 92.1%, $P = 0.8$) (Table 2). One sample missed by UA was identified as *Escherichia coli* (>100,000 CFU/ml); the three samples missed by 216Dx system included one *E. coli* (25,000 CFU/ml), one *Klebsiella oxytoca* (>100,000 CFU/ml), and one *Staphylococcus epidermidis* (>100,000 CFU/ml) sample.

The specificity of 216Dx was significantly higher than that of UA (82.7% versus 63.8%, $P < 0.001$). Overall, 31.0% (90/287) and 15.0% (43/287) of samples were FP by UA and 216Dx, respectively ($P \leq 0.0001$). A total of 127 samples were identified as contaminants by culture (Table 3). Among these samples, 46.0% (58/127) were detected as positive by UA versus 27.0% (34/127) by 216Dx. Additionally, among the 42.0% (122/287) culture-negative samples, 93.0% (112/122) were detected as TN by 216Dx and was significantly higher than the number of samples detected as TN by UA (74.0%, 90/122) ($P \leq 0.001$).

In this study, 31.0% of samples (89/287) were found to be discrepant between UA and 216Dx results, of which 69 samples tested as UA positive and 216Dx negative and 20 samples tested as UA negative and 216Dx positive. Among the 69 UA-positive, 216Dx-negative samples, 59.0% (41/69) were contaminant, 38.0% (26/69) were culture negative, and 4.0% (3/69) were culture positive. Among 20 UA-negative, 216Dx-positive

TABLE 2 Performance of urinalysis and BacterioScan 216Dx

Assay	No. of specimens with result:				Sensitivity (% [95% CI[a]])	Specificity (% [95% CI])	PPV (% [95% CI])	NPV (% [95% CI])	Accuracy (%)
	TP	FP	TN	FN					
UA	37	90	159	1[b]	97.3 (84.5–99.8)	63.8 (57.5–69.7)	29.1 (21.5–38.0)	99.3 (96.0–99.9)	68.0
216Dx	35	43	206	3[c]	92.1 (77.5–97.9)	82.7 (77.3–87.1)	44.8 (33.7–56.5)	98.6 (95.5–99.6)	84.0

[a]CI, confidence interval.
[b]*E. coli*, >100,000 CFU/ml.
[c]*K. oxytoca*, >100,000 CFU/ml; *S. epidermidis*, >100,000 CFU/ml; and *E. coli*, 25,000 CFU/ml.

TABLE 3 Comparison of bacterial culture results with those of Bacterioscan 216Dx and urinalysis

Instrument result	Culture results (n = 287) (n [%])		
	Pos (n = 38)	Neg (n = 122)	Contamination (n = 127)
216Dx pos (n = 78)	35 (92.0)[a,b]	9 (7.0)[c]	34 (27.0)[d]
216Dx neg (n = 209)	3 (8.0)	113 (93.%)	93 (73.0)
UA pos (n = 127)	37 (97.0)	32 (26.0)	58 (46.0)
UA neg (n = 160)	1 (3.0)	90 (74.0)	69 (54.0)

[a]MALDI-TOF identification (ID) passed, 27/35 (77%).
[b]MALDI-TOF ID failed, 8/35 (23.0%).
[c]MALDI-TOF ID failed, 9/9.
[d]MALDI-TOF ID failed, 34/34.

samples, 80.0% (16/20) were contaminant, 15.0% (3/20) were culture negative, and 5.0% (1/20) were culture positive.

We also attempted to identify all 216Dx-positive samples by MALDI-TOF MS. A total of 78 samples were presumptive positive by 216 Dx, of which 35 were culture positive. MALDI-TOF MS accurately identified the uropathogen in 27/35 (77.0%) urine-TSB sediment processed samples. A total of 6/8 urine samples not identified by MALDI-TOF were ≤50,000 CFU/ml, and 2/8 urine samples were ≥100,000 CFU/ml. Samples that were either negative or found to be contaminated by culture showed no peak by MALDI-TOF MS.

Escherichia coli was the most predominant (31/38, 82.0%) among all the uropathogens isolated by culture, ranging from 12,000 CFU/ml to >100,000 CFU/ml (Table 4). A total of four uropathogens were isolated along with a second organism with lower colony count (<10,000 CFU/ml). *Proteus mirabilis* was isolated along with another Gram-negative rod (50,000 CFU/ml and 2,000 CFU/ml), *Streptococcus agalactiae* with *Staphylococcus* species (50,000 CFU/ml and 9,000 CFU/ml), *Enterobacter cloacae* with *Staphylococcus* species (25,000 CFU/ml and 2,000 CFU/ml), and *E. coli* with coagulase-negative *Staphylococcus* species (25,000 CFU/ml and 2,000 CFU/ml).

DISCUSSION

Urinary tract infection is one of the most frequently occurring infections in patients of all ages. Consequently, most of the workload in the clinical microbiology laboratory involves urine culture work-up. Since urine culture turnaround time is between 24 and 48 hours, clinicians often use UA as a screening tool in a point-of-care setting, for which results can be obtained between 10 and 60 min, based on the testing methods. However, the sensitivity and specificity of UA are variable among different patient populations. A better, cost-effective alternative screening tool would be beneficial for patient management. In this study, we found that the sensitivity of UA (97.3%) and

TABLE 4 Distribution of uropathogens identified by bacterial culture and MALDI-TOF and their correlation with BacterioScan 216Dx and urinalysis results

Pathogen	No. of isolates identified by the following CFU/ml:		
	10,000–49,000	50,000–99,000	>100,000
E. coli	7[a]	1	23[b]
S. epidermidis	0	0	2[c]
E. cloacae	1	0	0
K. pneumoniae	0	0	1
K. oxytoca	0	0	1[d]
S. agalactiae	0	1	0
P. mirabilis	0	1	0
Total	8	3	27

[a]1/7 neg by 216Dx.
[b]1/23 missed by UA.
[c]1/2 missed by 216Dx.
[d]1/1 missed by 216Dx.

216Dx (92.1%) were comparable ($P = 0.8$) but that the specificity is much higher for 216Dx (83.0%) than for UA (64.0%) ($P < 0.001$). Both assays have a high negative predictive value (>98.5%). Overall, 216Dx demonstrated superior performance to UA in our study using unpreserved, clean-catch urine samples obtained from a pediatric population.

In clinical laboratories, UA has long been used as a screening tool for presumptive diagnosis of UTI, with variable sensitivity and specificity. Tzimenatos et al. reported that the sensitivity and specificity of UA were 94.0% and 91.0%, respectively, in young febrile children aged <60 days (12). In contrast, Reardon et al. reported that compared to culture, the sensitivity and specificity of UA were 64.0% and 91.0%, respectively, in febrile children <90 days of age (13). In our study, we used the following three criteria to categorize UA as either positive or negative: (i) nitrite, (ii) leukocyte esterase, and (iii) white blood cell count. Gram-negative bacteria convert dietary nitrate to nitrite. A positive nitrite test can be used to indicate presumptive bacteriuria in patients, with variable sensitivity and specificity (39.0% to 93.0%) (16–18). In our study, a total of 9 samples were positive for nitrite, and a Gram-negative bacterium was isolated from all 9 samples at >100,000 CFU/ml. Leukocyte esterase (LE), produced by neutrophils, is an indirect assay to measure pyuria and can be rapidly detected by using a dipstick assay. Like the nitrite assay, the sensitivity and specificity of the LE assay are variable and range from 74.0% to 96.0% and 94.0% to 98.0%, respectively (15). In our study, the sensitivity of LE was 92.0%, but the specificity was only 65% which is lower than previous reports of 94.0% to 98.0%. Pyuria is defined as the presence of an increased number of white blood cells in urine and is a useful marker for presumptive UTI. However, the threshold for pyuria is debatable. A meta-analysis on screening tests for UTI in children found that at ≥5 white blood cell (WBC)/hpf, pooled sensitivity and specificity were 67.0% and 21.0%, respectively (19). The same study also found an increased sensitivity to 77.0% when the threshold was set to >10 WBC/hpf. In our study, we used ≥5 WBC/hpf as a threshold for pyuria. At this threshold, the sensitivity and specificity were 81.6% and 76.0%, respectively.

Laser scattering technology has been in use for many years. The first use of this technology dates back to the 1980s, when Hale et al. used it for rapid screening for bacteriuria (20). Recently, this technology has been modified, FDA-cleared, and marketed by BacterioScan. Since then, few clinical laboratories have validated the performance of this system. According to the FDA decision summary, the sensitivity and specificity of 216Dx is 97.7% and 72.1, respectively, when bacterial load by colony count on culture plate of 50,000 CFU/ml was considered the cutoff (14). However, the sensitivity drops to 92.6% at 10,000 CFU/ml. In another independent study, using both preserved and unpreserved urine samples obtained from patients >90 days of age, the authors found that the sensitivity and specificity of 216Dx were 96.5% and 72.0%, respectively (21). The authors also reported a high negative predictive value (98.8%) and concluded that due to its high NPV, 216Dx can be used as a screening tool for presumptive diagnosis of UTI. In our study at 10,000 CFU/ml, the sensitivity, specificity, positive predictive value, and negative predictive value were 92.1%, 82.7%, 44.8%, and 98.6%, respectively. Recently, using urine samples obtained mostly from in-patients and all age-groups, Roberts et al. found overall better performance of 216Dx than UA (22). According to this study, the sensitivity and specificity of 216Dx versus UA was 76.0% versus 59.0% and 84.0% versus 87.0%, respectively (22). The sensitivity of 216Dx was higher in our study, perhaps due to a different procedure for sample transportation and patient population. While Roberts et al. used boric acid as a preservative for sample collection, all our urine samples were without any preservative. Another major difference was that our study was limited to only the pediatric population.

The strength of 216Dx lies in early detection of contamination and true-negative samples. In order to reduce the rate of contamination, several factors need to be considered, such as urine collection, preservation, storage, transport, and laboratory methods (23). Yet, detecting a high rate of contamination is not uncommon. In our study, urine specimens that subsequently turned out to be contaminated by culture

were screened as negative by 216Dx (73%) at a higher rate than UA (54%), thereby demonstrating that 216Dx had a better potential to screen out more contaminated urine samples early and reduce unnecessary work-up by almost 19.0%. Similarly, the performance of 216Dx was better in detecting culture-negative samples than UA (93.0% versus 74.0%). Taken together, 216Dx could improve the accuracy of calling culture-negative and contaminated samples by 38.0%, relative to UA. For laboratories equipped with a MALDI-TOF instrument, there could be other potential advantages to using 216Dx as a screening tool, followed by species-level bacterial identification directly from positive urine-TSB mixture within 30 minutes of initial 216Dx results. In an earlier study, Montgomery et al. had a 83.6% (46/55) success rate to obtain species-level identification by MALDI-TOF directly from a 1.0-ml urine-TSB mixture, of which 40 samples were monomicrobial by culture (21). In this study, we attempted to identify the pathogens directly from urine-TSB sediments after the completion of 216Dx screening and accurately identified bacteria at the species level in 77.0% of samples. However, 8 samples were missed by this approach, perhaps due to the presence of a low density of microorganisms (6/8 had ≤50,000 CFU/ml). It is interesting to note that unlike a previous study (21), all of the 216Dx presumptive positive urine specimens that subsequently turned out to be contamination by urine culture failed to produce any peak or identification by MALDI-TOF.

As stand-alone screening assays and due to their high negative predictive value, UA and 216Dx could potentially remove 55.0% (159/287) and 72.0% (206/287) of negative/contaminated samples from culture work-up, respectively. However, by using both assays as a two-step screening tool (UA-positive samples reflexed to 216Dx), hypothetically, 80.0% (229/287) of all samples in our study could be removed from routine culture work-up within 4 hours of initiation of sample testing (approximately 1 hour for UA assay followed by 3 hours of 216Dx assay), thus significantly decreasing turnaround time (TAT) from 24 to 48 hours to 4 hours for negative and contaminated samples. However, this approach would have missed 4 true positive samples (1.0%) as well (3 by 216Dx and 1 by UA) in our study. The simultaneous use of UA and 216Dx can further reduce the total TAT from 4 hours to 3 hours but may add to laboratory costs due to the use of both tests on all specimens.

Urine culture positivity rate was 13.0% in our study, which is close to earlier reports (13.0% to 19.0%) (21, 24). The uropathogens identified in our study also represent the typical urine culture results. The gram-negative bacterium *E. coli* was the most common uropathogen (82.0%) identified in our study, which is similar to previous reports (16, 25, 26). However, we have a few limitations in our study. First, we found only three Gram-positive bacteria (2 *S. epidermidis* and 1 group B *Streptococcus* isolate) in our study, and it may not represent the complete spectra (such as *Staphylococcus saprophyticus* and *Enterococcus faecalis*) of Gram-positive bacteria responsible for UTI in children (27). Second, we used only midstream clean-catch urine samples, and no other collection types, such as catheter, Foley, and suprapubic aspirates, were tested.

In summary, the overall performance of the BacterioScan 216Dx instrument is superior to that of UA. 216Dx can be used as an alternative screening tool to UA to rule out bacterial infection in children. Compared to culture, the faster turnaround time (3 hours) of 216Dx coupled with rapid identification by MALDI-TOF has the potential to reduce unnecessary antibiotic use, improve patient management, and reduce health care-related costs.

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