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Brief communication (Original)

A flow cytometric urine analyzer for bacteria and white blood cell counts plus urine dipstick test for rapid screening of bacterial urinary tract infection

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Background: Bacterial urinary tract infection (UTI) is one of the most common patient problems that have no reliably definite diagnosis. The gold standard urine culture is usually delayed and increases laboratory workload.
Objectives: To find a rapid method for the screening of bacterial urinary tract infection, the performance of four urinalysis parameters from automated urine dipstick test and flow cytometry were evaluated against the urine culture method.
Methods: Urine cultures were performed on 372 routine specimens of suspected UTI. Urine dipstick tests were performed using an automated reader. An automated urine particle analyzer was used for quantitative counting of bacteria and white blood cells.
Results: For screening of UTI, urinary bacteria count ≥14.2 cells/μL gave the highest sensitivity of 95.76% and 44.88% specificity.
Conclusion: We suggest using urinary bacteria count for screening of UTI. This method can reduce the laboratory workload for processing urine culture by 30.64%.

Keywords: Flow cytometry, urinalysis, urine dipstick, UTI

Bacterial urinary tract infection (UTI) is one of the most commonly reported medical problems and can cause serious complications in children, elderly people, diabetics, and immunocompromised patients [1, 2]. The gold standard for diagnosing UTI is by quantitative urine culture. The definition of significant bacteriuria for diagnosis is usually set at 10^5 Colony Forming Unit (CFU)/mL from urine culture [3-6]. However, the test is not available in primary care unit. In an outpatient setting, urine culture is not always applicable and the physician has to rely on urinalysis for presumptive diagnosis of UTI. Therefore, we evaluated urinalysis parameters for the improvement of UTI screening.

As half of the submitted urine cultures have negative results and the work done to perform these tests generates a significant workload and cost for the laboratory [7]. Furthermore, urinalysis is used as a screening test to reduce these unnecessary cultures. Urine microscopy including urine Gram stain and white blood cell (WBC) count has been generally adopted as tests for analyzing pyuria and bacteriuria. Nevertheless, these manual methods are time consuming, labor-intensive and, difficult to reproduce. Additionally, they are insensitive in cases having low bacterial concentration [8-17].

The urine dipstick has long been recognized as a capable screening test [18-23]. A positive result from either leukocyte esterase (LE) or nitrite (NIT) can be used for screening of UTI [18, 19, 23]. However, LE may show a false negative result in specimens with an elevated specific gravity, protein or glucose [19-20].The nitrite test alone has high specificity but low sensitivity [21].The other disadvantage is that the test requires a first morning urine and may not be associated with some pathogens such as *S. saprophyticus* [22].

Automated urine particle analyzer has recently become available. They combine flow cytometry with fluorochrome dyes for impedance analysis. This analyzer allows discrimination and quantification of

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bacteria, erythrocytes, leukocytes, epithelial cells, casts, and flagging of crystals, fungi, and sperm in the urine specimen. Furthermore, it can be used as a screening test for UTI [24-28].

Nevertheless, there is a continuing debate on which test or combination of tests defines the best for diagnosis of UTI [19, 21]. In this study, we evaluated the individual and combination of four urine parameters for screening UTI in significant bacteriuria.

Material and method

Three hundred seventy two random midstream urine specimens were collected from inpatients and outpatients at Ramathibodi Hospital, Bangkok between September and November 2010. The specimens from other urine collection methods were excluded. Urine specimens were collected in a sterile cup for urine culture and a clean disposable cup for urinalysis. Specimens were not centrifuged and did not contain any preservatives. They were processed within 2 hours of collection.

The study was reviewed and approved by the local ethical review board for research in human subjects and was in accordance with the Helsinki Declaration of 1975.

Quantification of urine culture

The urine specimens were inoculated by filter paper method on 5% blood agar plates for quantification [29]. Positive urine cultures were defined as having a colony count ed10^5 CFU/mL. Specimens showing positive culture of more than 2 bacterial species, without a predominant pathogen, were classified as contaminated. Other organisms such as fungi were excluded.

Urine dipstick tests

Urine dipstick test (Urisys 2400 Cassette, Roche Diagnostics, Germany) was performed using the automated Urisys 2400 (Roche Diagnostics, Germany).

Automated flow cytometric urine analysis

After dipstick testing, urine sample tubes were transferred to the automated urine analyzer (Sysmex UF-1000i, Sysmex, Kobe, Japan). The automated urine particle analyzer UF-1000i uses Flow Cytometry (FCM) Technology to obtain the parameters of forward scattered and forward fluorescent light of urine cells. After specific substances in the cells are given fluorescent staining and placed in suspension, they are then covered in sheath fluid and ejected through a nozzle in a single row. Here each urine cell is illuminated by tightly focused laser beam. The individual cells fluoresce and scatter light to varying degrees. It is the analysis of these electrical signals which allows each urine cell to be discriminated by generating a one–dimensional histogram, based on fluorescent intensity, and a two–dimensional scatter gram, based on fluorescent intensity and scatter light intensity.

The light scattered from the forward direction to lateral directions from the laser light source is called Scattered Light. It reflects the size and the surface condition of cells in proportion to the luminosity. It reflects the size and the surface condition of cells in proportion to the luminosity. The fluorescent light emitted from the stained urine cell reflects the quantitative cell surface and intracytoplasmic properties, and properties of the nucleus (amounts of RNA and DNA) due to the properties of the fluorescent-labeled antibody and the fluorescent pigment.

Based on the principles of flow cytometry, which classified the five organized elements of urine sample as RBC (Red Blood Cell), WBC (White Blood Cell), EC (Epithelial Cell), CAST (Cast), and BACT (Bacteria) and displayed them quantitatively. Urine cells are classified by using a classification algorithm [25-29]. Thus, white blood cell (WBC) and bacteria (BAC) count were generated.

The urine dipstick and flow cytometry analysis were performed individually and objectively with different automated instruments. Separated results from each instrument were combined in laboratory information software. Samples giving discordant results were reevaluated by manual microscopic sediment examination to ensure accuracy of urinalysis. Laboratory technicians were blinded to the clinical status of samples.

Statistic analysis

Data for each patient including the demographic details, LE, NIT, WBC and BAC count, urine culture, and the bacteria strains isolated, were recorded on a spreadsheet.

In order to establish their cut-off and the diagnostic performance of the evaluated parameters, Receiver Operating Curves (ROC) of the BAC and WBC count were evaluated. Besides ROC, Sensitivity (SE),

Specificity (SP), Positive Predictive Value (PPV), Negative Predictive Value (NPV) were calculated using STATA 11.1 Special Edition (Stata Corp, Texas, USA). SPSS 17.0 (IBM Corp, NY, USA) were used for normal distribution evaluation and the calculation of correlation coefficient and *p*-value.

Result

Three hundred seventy two urine specimens were obtained, and 217 (57.37%) were outpatients, 158 (42.63%) were inpatients. Of these, 167 were men (mean age = 55.3±20.01), and 205 were women (mean age = 59.75±20.74).

One hundred and eighteen specimens (31.72%) showed a positive result of $\geq 10^5$ CFU/mL. Single pathogen was identified in 79 specimens. There were 12 specimens with two pathogens and 27 specimens were contaminated. The bacterial strains in this study were shown in **Table 1**.

Mean BAC counts were 374 cells/μL and 19554 cells/μL in negative and positive specimens respectively. Mean WBC counts for negative and positive specimens were 103 cells/μL and 686 cells/μL respectively. The correlation coefficient (r) for BAC count and culture was 0.625 ($p < 0.0001$).

ROC curves for WBC and BAC count were shown in **Figure 1**, and areas under the curve (AUC) were 0.74 (95%CI, 0.68-0.80) and 0.88 (95%CI, 0.84-0.92) respectively. There was a statistically significant difference between the area of two ROC curves ($p < 0.0001$). The cutoff was of 6.7 cells/μL for the WBC count. It gave a sensitivity of 81.36% and a specificity of 41.73% was selected. Likewise, a cutoff of 14.2 cells/μL for the BAC count gave a sensitivity of 95.76% and a specificity of 44.88%.

The diagnostic performances of the four urine parameters evaluated; LE, NIT, WBC, and BAC count were shown in **Table 2**. The sensitivity, specificity, positive predictive value, and negative predictive value of individual parameter were calculated. Furthermore, diagnostic performances of the combination of two, three, or four parameters were also calculated. The BAC count showed the best sensitivity as an individual parameter. The combination of either WBC count or BAC count of equal or more than the selected cutoff values gave the highest sensitivity. Combining three or four parameters did not increase the sensitivity of testing.

Table 1. Bacteria obtained from culture of 91 positive urine specimens

Bacteria	Number	%
Escherichia coli	34	33.01
Escherichia coli ESBL	16	15.53
Acinetobacter baumannii	1	0.97
Enterococcus species	12	11.65
Klebsiella pneumoniae	11	10.68
Klebsiella pneumoniae ESBL	2	1.94
Pseudomonas aeruginosa	11	10.68
Enterobacter cloacae	4	3.88
Proteus mirabilis	2	1.94
Morganella morganii	2	1.94
Aeromonas jandaei	1	0.97
Citrobacter freundii	1	0.97
Providencia rettgeri	1	0.97
Staphylococcus aureus	1	0.97
Coagulase-positive staphylococci	1	0.97
Coagulase-negative staphylococci	1	0.97
Stenotrophomonas maltophilia	1	0.97
Lactobacillus species	1	0.97
Flavobacterium species	1	0.97

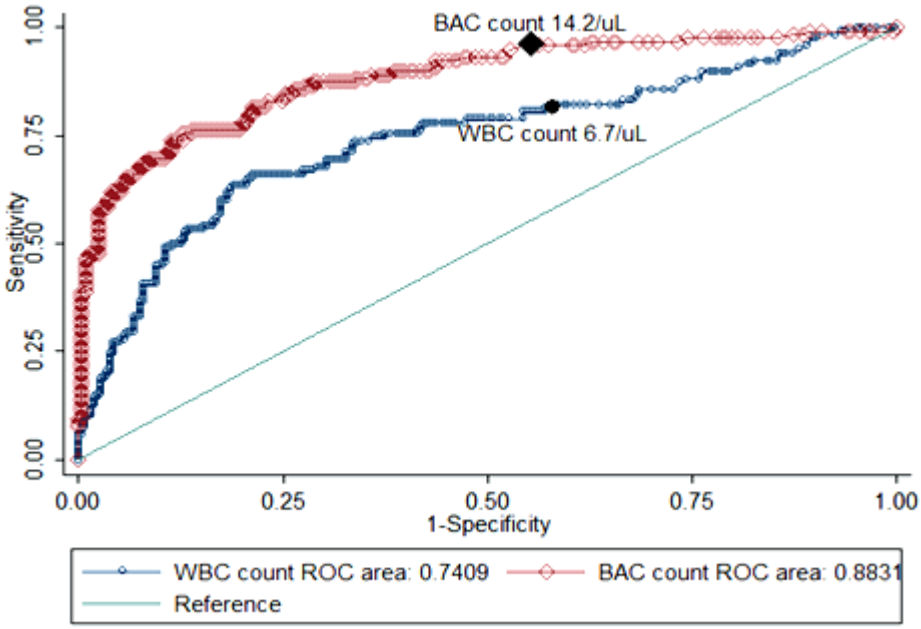

Figure 1. The ROC curve for BAC and WBC count obtained on Sysmex UF-1000i for 91 positive urine cultures at a cutoff of $\geq 10^5$ CFU/mL

Discussion

Because of the disadvantages of urine culture plus the difficulty in differentiating colonization and contamination from true infection, urinalysis was used for UTI screening. In this study, we used an automated urine dipstick test method and an automated flow cytometry method to evaluate the individual and combination of LE, NIT, WBC count, and BAC count for screening UTI.

The BAC count and WBC count did not follow a normal distribution (data not shown) but the BAC counts showed good correlation with the urine cultures. The bacterial strains identified were similar in frequency to those of Wilson et al [30], and that comprising of *Escherichia coli*, as the majority, followed by *Klebsiella* and *Enterococcus* species.

For screening, the cutoff for BAC count at 14.2 cells/µL, which has a sensitivity of >95% sensitivity, was selected. This cutoff produced only five false negative and 114 true negative cases. This could reduce the unnecessary urine culture by 30.4%. Our BAC count cutoff values were lower than those of the other studies [31-36] using the previous model of urine flow cytometer (UF-100). This could be due to the development of a new analytical channel that has higher capacity to exclude debris, mucus, and cell fragments from urine particles thus increasing the sensitivity and specificity of BAC counting [24, 27]. It is useful to mention that the calibrated loop urine quantification method was used by other studies [24-28, 37], while the filter paper method was used in this study. In addition, the urine culture cutoff from 10^4 to 10^6 CFU/mL was used for diagnosis of UTI in other studies [24-28, 37]; the cutoff of ee10^5 CFU/mL was used in this study. In summary, the use of filter paper urine quantification method and cutoff of ee10^5 CFU/mL could contribute to the fact that the BAC count cutoff in this study seemed to be the lowest compared to other studies. The cutoff for WBC count, which give a sensitivity of >95%, showed a very low specificity of <20%. Therefore, a cutoff of 6.7 cells/µL, which gave a likelihood ratio of >2, was selected instead. This cutoff gave a sensitivity of 81.36% and a specificity of 41.73% specificity.

The cutoff for WBC count in this study was lower than other studies. The cutoff used for positive urine culture and urine quantification method could be explained by the WBC count cutoff points and arbitrary selection of prevalence and the population being studied [24-28, 37].

The sensitivity and specificity of LE and NIT observed in this study was comparable to those of the other studied [23, 30]. NIT alone had a high specificity but low sensitivity [21], which can be used for diagnostic purposes rather than screening. LE and WBC count also gave a low sensitivity. Therefore,

Table 2. Diagnostic performance of four urinalysis parameters in 91 positive urine specimens

	Colony count at ≥10^5 CFU/mL							
	Sensitivity (%)	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**TP**	**TN**	**FP**	**FN**
One parameter								
Le+	67.8	62.99	45.98	80.81	80	160	94	38
Ni+	27.97	97.64	84.62	74.47	33	248	6	85
WBC+	81.36	41.73	39.34	82.81	96	106	148	22
BAC+	95.76	44.88	44.66	95.8	113	114	140	5
Two parameters								
Le+ or Ni+	72.03	62.6	47.22	82.81	85	159	95	33
Le+ or WBC+	82.2	38.58	38.34	82.35	97	98	156	21
Le+ or BAC+	96.61	35.43	41.01	95.74	114	90	164	4
Ni+ or WBC+	81.36	41.73	39.34	82.81	96	106	148	22
Ni+ or BAC+	95.76	44.88	44.66	95.8	113	114	140	5
WBC+ or BAC+	96.61	27.95	38.38	94.67	114	71	183	4
Le+ and Ni+	23.73	98.03	84.85	73.45	28	249	5	90
Le+ and WBC+	66.95	66.14	47.88	81.16	79	168	86	39
Le+ and BAC+	66.95	72.44	53.02	82.51	79	184	70	39
Ni+ and WBC+	27.97	97.64	84.62	74.47	33	248	6	85
Ni+ and BAC+	27.97	97.64	84.62	74.47	33	248	6	85
WBC+ and BAC+	80.51	58.66	47.5	86.63	95	149	105	23
Three parameters								
Le+ or Ni+ or WBC+	82.2	38.58	38.34	82.35	97	98	156	21
Le+ or Ni+ or BAC+	96.61	35.43	41.01	95.74	114	90	164	4
Ni+ or WBC+ or BAC+	96.61	27.95	38.38	94.67	114	71	183	4
Le+ and Ni+ or WBC+	81.36	41.73	39.34	82.81	96	106	148	22
Le+ and Ni+ or BAC+	95.76	44.88	44.66	95.8	113	114	140	5
Le+ and WBC+ or Ni+	71.19	65.75	49.12	83.08	84	167	87	34
Le+ and WBC+ or BAC+	96.61	37.01	41.61	95.92	114	94	160	4
Le+ and BAC+ or Ni+	71.19	72.05	54.19	84.33	84	183	71	34
Le+ and BAC+ or WBC+	82.2	40.16	38.96	82.93	97	102	152	21
Ni+ and WBC+ or Le+	72.03	62.6	47.22	82.81	85	159	95	33
Ni+ and WBC+ or BAC+	95.76	44.88	44.66	95.8	113	114	140	5
Ni+ and BAC+ or Le+	72.03	62.6	47.22	82.81	85	159	95	33
Ni+ and BAC+ or WBC+	81.36	41.73	39.34	82.81	96	106	148	22
WBC+ and BAC+ or LE+	82.2	47.64	42.17	85.21	97	121	133	21
WBC+ and BAC+ or Ni+	71.19	72.05	54.19	84.33	84	183	71	34
Le+ and Ni+ and WBC+	23.73	98.03	84.85	73.45	28	249	5	90
Le+ and Ni+ and BAC+	23.73	98.03	84.85	73.45	28	249	5	90
Le+ and WBC+ and BAC+	66.1	74.02	54.17	82.46	78	188	66	40
Ni+ and WBC+ and BAC+	27.97	97.64	84.62	74.47	33	248	6	85
Four parameters								
Le+ or Ni+ or WBC+ or BAC+	96.61	26.38	37.87	94.37	114	67	187	4
Le+ and Ni+ and WBC+ or BAC+	95.76	44.88	44.66	95.8	113	114	140	5
Le+ and Ni+ and BAC+ or WBC+	81.36	41.73	39.34	82.81	96	106	148	22
Ni+ and WBC+ and BAC+ or Le+	72.03	62.6	47.22	82.81	85	159	95	33
(Le+ and Ni+) or (WBC+ and BAC+)	80.51	58.66	47.5	86.63	95	149	105	23
(Le+ and Ni+) or WBC+ or BAC+	96.61	27.95	38.38	94.67	114	71	183	4
(Le+ and WBC+) or (Ni+ and BAC+)	71.19	65.75	49.12	83.08	84	167	87	34
(Le+ and WBC+) or Ni+ or BAC+	96.61	37.01	41.61	95.92	114	94	160	4
(Le+ and BAC+) or (Ni+ and WBC+)	71.19	72.05	54.19	84.33	84	183	71	34
(Le+ and BAC+) or Ni+ or WBC+	96.61	27.95	38.38	94.67	114	71	183	4
Le+ and Ni+ and WBC+ and BAC+	23.73	98.03	84.85	73.45	28	249	5	90

LE = Leukocyte esterase, NIT = Nitrite, TP = True positive, TN = True negative, FP = False positive, FN = False negative
*WBC+ = WBC Count at 6.7/μL, BAC+ = Bacteria count at 14.2/μL

they were unsuitable as screening parameters. Being similar to other findings [24-28, 37], BAC count gave the highest sensitivity as shown in **Table 2**. However, Jolkkonen et al. separated the sample population by age and gender and used the difference of CFU count in each group and found that BAC count and WBC count in age- and gender-specific cutoff values was the most sensitive screening method [38]. Nevertheless, different sample population and criteria of UTI were used in their study, while a single criterion of 10^5 CFU/mL, which is more practical in routine laboratory screening, was used in this study. In addition, we did not exclude the contamination of urine culture and request a new sample. The automated flow cytometric urine particle analyzer was found to produce false negative result in gram-positive pathogens [24, 39]. However, in this study, we had two false negative results in gram-negative specimen. Twenty-four out of 27 contaminated specimens had a BAC count above our cutoff, showing that the automated urine analyzer could not distinguish contaminated specimen from true positive one.

When we combined two parameters, either a positive LE or NIT, a higher sensitivity was obtained as compared to LE or NIT alone. These were the same as results from previous research studies [18-19, 23]. The specificity of NIT was not increased even when combined with WBC count or BAC count. The combination of LE+ or WBC+ increased the sensitivity to 96.61% but there was an increase of 24 false positive cases. Comparatively, one false negative was decreased if it was based on BAC count alone. As with the combination of two parameters, a positive NIT with either a positive LE or WBC count, or a positive NIT with either a positive LE or BAC count, the combination of three or four parameters did not increase the sensitivity and specificity of testing. Therefore, a single parameter of BAC count has shown to be the best for UTI screening.

Conclusion

Urine culture is still needed in case of complicated UTI because bacterial identification and antibiotic susceptibility is necessary. We suggest using BAC count from automated flow cytometric urine analyzer for UTI screening. This rapid screening tool could eliminate 30.64% of a laboratory's workload and could reduce the unnecessary antibiotic use in true negative cases in an outpatient setting. Each laboratory needs to select their cutoff points for appropriate sensitivity or specificity.

Further evaluation with a larger sample size and within other patient population groups is required. History of symptoms and antibiotic use should also be considered.

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