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Original article

Customized cutoff limits for the sediMAX-2 automated analyzer reduce the number of urine culture tests

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Abstract. *Background and aim:* Urinary tract infections are highly prevalent in nosocomial and community settings. Their diagnosis, although costly and time-consuming, is crucial to avoid inappropriate treatments and/or clinical complications. In this context, automated analyzers have been developed and commercialized to screen and rule out negative urine samples. Adjustments of the manufacturers' suggested cutoff values might lead to substantial diagnostic and economic advantages. *Methods:* We retrospectively analyzed 776 urine samples from different individuals. 546 samples (training group) were used to optimize and develop new cutoff values. The remaining 230 samples (validation group) were used to validate the optimized cutoffs. All samples were subjected to urine culture, 17% resulted positive. *Escherichia coli* and *Enterococcus faecalis* were the two most frequently identified bacteria, 95 and 9 samples, respectively. *Results:* Two different cutoff levels were obtained. Cutoff-A (bacteria>110 and/or white blood cells> 15 cells/µL), showed the same sensitivity as the manufacturers' suggested cutoff, yet leads to a large reduction of the samples to be cultured. Cutoff-B (bacteria>50 and/or white blood cells>20 cell/µL), showed an almost 100% sensitivity by subjecting only ~70% of the samples to urine culture. *Conclusions*: Cutoff-A is a good compromise between sensitivity and specificity yet allowing economic advantages by reducing the number of urinary cultures. Cutoff-B relegates urinary tract infection misdiagnosis to a rare event without the need of culturing the entire batch of samples. We believe that clinical implementation of the proposed cutoffs will help other laboratories, using similar instrumentation, to reach their most convenient balance between sensitivity and economic needs. (www.actabiomedica.it)

Key words: SediMax, urinary tract infection, automated urinalysis, customized cutoff

Introduction

Urinary tract infections (UTI) are the most common infection worldwide, affecting 150 million people annually (1–4). Clinical symptoms are often unspecific (5) and the gold standard in UTI diagnosis is considered quantitative urine culture (UC) (6). However, UC is costly (7), requires 24-48 hours before results' availability (8) and, on average, approximately 80% of the samples yield a negative result. Broad-range antibiotics are then prescribed for most patients before diagnosis, promoting antibiotics use and resistance (9). Thus, alternative and reliable strategies able to detect the urinary infection as quickly as possible are sought to rapidly treat patients and to avoid unnecessary and expensive UC tests (10,11). Methods like the use of chemical dipsticks detecting leukocyte esterase and/or nitrites proved to be useful (12) yet, they produce several false positive and false negative results (1,13,14). Several automated urinalysis systems have been commercialized over the past few years with the aim of providing a rapid and reliable screening method (2,15,16). An example is the SediMAX-2, which is able to capture and recognize images of monolayered

urine sediment in a cuvette with a digital camera. Such instrument is used, routinely, at the Laboratory Medicine Service of the San Raffaele Hospital (Milan, Italy), in association with the Aution Max AX-4030, an automated urine test-strip analyzer. The latter and the SediMax-2 have been thoroughly evaluated in the past (17–19) and both proved to be reliable equipment.

Bacterial (BAC) and white blood cells (WBC) count, together with the presence or absence of nitrite, are the variables used to discriminate between positive and negative samples according to the manufacturer's suggested cutoff values. The aim of this study was to extrapolate new sets of cutoff values (different from the manufacturers' suggested ones), based on routine laboratory results and able to maximize both the sensitivity and the negative predictive values (NPV) of the test. A total of 776 urine samples were collected in two different sessions. The first group (training group: 546 samples) was used to estimate the new cutoff values using quantitative UC as the gold standard. The efficacy of the extrapolated cutoffs in predicting UTI positivity and negativity was then evaluated by using additional 230 urine samples (validation group).

Customized cutoffs, different from the manufacturers' suggested ones, will improve urine samples screening efficacy in the clinical laboratory. Furthermore, they can be developed with the aim of reaching the desired compromise between diagnostic efficacy and economic needs, which may not be the same in every laboratory.

The reliable identification of negative results, without the need of UC, will improve turnaround times and throughput as well as reduce the workload and the inherent costs of UTI diagnosis. Furthermore, a reliable classification of negative urine samples will reduce the inappropriate use of antibiotics, which is associated with poorer clinical and economic outcomes (20–22).

Material and methods

SediMAX-2

The sediMAX-2 (Menarini diagnostic, Florence, Italy), a fully automated walk-away analyzer, requires 2 mL of native urine in a test tube. 200 µL are pipetted in the cuvette and centrifuged for 10 s to force the urinary particles at the bottom of the cuvette. A built-in camera takes 15 digital images (corresponding to 2.4 µL of native urine) from different locations with an approximate image magnification of 400 × enlargement. A client computer is responsible for the particle recognition process. Only bacteria (BAC) and white blood cells (WBC) counts were used for this study. The manufacturers' suggested cutoffs used to discriminate for UTI are 9 and 90 cell/µL for WBC and BAC respectively. These cutoffs were not derived from a normal population study but selected by the manufacturer in order to provide the best diagnostic sensitivities and specificities (17).

Aution Max AX-4030

The Aution Max AX-4030 (Menarini diagnostic, Florence, Italy) exploit urine strips to measure glucose, proteins, bilirubin, pH, blood, urobilinogen, ketones, nitrite, leukocyte esterase, specific gravity, turbidity and color-tone. Only nitrite results were considered for this study.

Collection of urine specimens

776 urine samples (546 for the training group and 230 for the validation group), were collected in sterile containers, from both inpatients and outpatients (approximately 20% and 80% respectively). Samples from 275 females and 271 males (1 to 93 years, median age 56 years) were collected for the training group whereas samples from 118 females and 112 males (2 to 95 years; median age 56 years) were collected for the validation group. Samples were collected between the first week of December 2022 (training group) and in the last week of January 2023 (validation group). Catheterized patients were excluded from the study. Samples were tested within 3 h of their receipt in the laboratory. All patients or their legal representative gave an informed consent authorizing the use of their anonymously collected data for the research studies (article 9.2.j of the EU general data protection regulation 2016/679 [GDPR]), according to the San Raffaele Hospital internal policy (IOG075/2016).

Urine culture and analysis

Cultures were performed by inoculating urine samples on a chromIDCPS (bioMérieux, Florence, Italy) agar plate using a 1-µl loop and were incubated overnight at 37°C. Quantification in CFU/ml was performed by a manual count of the colonies growing on the agar plate multiplied by the corresponding dilution factor. Samples were considered positive if growth ≥105 CFUs/ml. Samples with three or more different types of colonies were considered contaminated and not included in the study (37 samples). Throughout the paper, positive UC samples have been associated with UTI without clinical review. Thus, patients with asymptomatic bacteriuria (ASB) were also included.

Statistical analysis

Statistical analyses were performed by SPSS statistical software v.17.0 (SPSS Inc., Chicago, USA). Sensitivity and specificity were calculated as the number of true positives/number of positive outcomes (urine culture positivity) and as the number of true negatives/number of negative outcomes (urine culture negativity), respectively. Negative predictive value (NPV) and positive predictive value (PPV) were calculated as the number of true negatives/total number of negatives and as the number of true positives/total number of positives, respectively. Performances of BAC and WBC in predicting UC positivity were assessed by plotting receiver operating characteristic (ROC) curves, with 95% confidence bounds, and by calculating the area under the ROC curve (AUC), using MedCalc Statistical Software version 9.2.1 (MedCalc Software bvba, Ostend, Belgium).

Results

Overall samples

Of the 776 samples tested 132 (17%) were culture positive. The percentage is very similar to that (18%) observed in previous studies (1,23). Table 1 shows

Table 1. Urine culture results in the training and validation group, and type of strains identified.

	Training group (%)	**Validation group (%)**	**Total (%)**
Total / positive	546 / 96[a] (17.6)	230 /36 (15.7)	776 / 132 (17.0)[a]
Strain			
Candida albicans	1 (1.0)	-	1 (0.7)
Citrobacter koseri	1 (1.0)	-	1 (0.7)
Escherichia coli	69 (69.0)	26 (72.2)	95 (69.9)
Enterococcus faecium	1 (1.0)	-	1 (0.7)
Enterococcus faecalis	7 (7.0)	2 (5.5)	9 (6.6)
klebsiella oxytoca	2 (2.0)	-	2 (1.5)
klebsiella pneumoniae	7 (7.0)	1 (2.8)	8 (5.9)
Morganella morganii	1 (1.0)	-	1 (0.7)
Proteus mirabilis	1 (1.0)	1 (2.8)	2 (1.5)
Pseudomonas aeruginosa	3 (3.0)	1 (2.8)	4 (3.1)
Serratia marcescens	1 (1.0)	-	1 (0.7)
Streptococcus Agalactiae	6 (6.0)	2 (5.5)	8 (5.9)
Enterobacter aerogenes	-	1 (2.8)	1 (0.7)
Enterobacter cloacae	-	1 (2.8)	1 (0.7)
Enterobacter hormaechei	-	1 (2.8)	1 (0.7)

[a]Four samples in the training group showed the concomitant presence of two types of strains, bringing the number of strains to 100 (in 96 samples). For the same reason the total number of strains is 136.

the bacterial strains associated with the positive culture. The two most common strains were *Escherichia coli* (70%, 95 samples) and *Enterococcus faecalis* (7%, 9 samples). The results are in agreement with a previous study from Kim et al. where out of 7443 samples analyzed Escherichia coli and Enterococcus faecalis were found, respectively, in 67% and 6% of the samples (1). Four samples showed the concomitant presence of two different types of colonies, bringing the total number of bacterial strains to 136 (Table 1).

Training group

Of the 546 samples analyzed, 96 (17.6%) were positive. The Aution Max AX-4030 detected nitrite in 45 samples and, after UC, 43 resulted positive. This was consistent with a sensitivity of 43.8% and a very high specificity of 99.3%. In other words, the presence of nitrite was almost always associated with UTI (according to UC) but its absence does not necessarily exclude the presence of UTI.

By using the manufacturers' suggested cutoffs (BAC>90 cell/μL and/or WBC>9 cell/μL), meaning that any sample exceeding at least one of the two parameters would be considered at risk of UTI and subjected to UC, the specificity and sensitivity were respectively 56.2% and 97.9%. This cutoffs combination showed a PPV of 32.3% and a NPV of 99.2% (Table 2), thus, 46.7% of the UC could be avoided while only 0.8% of the urine samples with BAC<90 cell/μL and/or WBC<9 cell/μL became culture positive. In other words, by applying the manufacturers' cutoff combination, out of 546 samples, two individuals having UTI (according to UC), were misdiagnosed based on the sediMAX-2 results.

ROC curves were calculated for both BAC and WBC based on the UC results. The areas under the curve (AUC) were 0.847 and 0.838 for BAC and WBC respectively (Figure 1). The ROC curves for BAC and WBC showed the highest combination of sensitivity and specificity at 228.5 and 14.5 cell/μL, respectively. These values were combined together to obtain a new cutoff (BAC>228.5 cell/μL and/or WBC>14.5 cell/μL) which yielded a specificity of 78.2%, a sensitivity of 89.6% and a PPV and NPV of 46.7% and 97.2%, respectively (Table 2). Thus, using

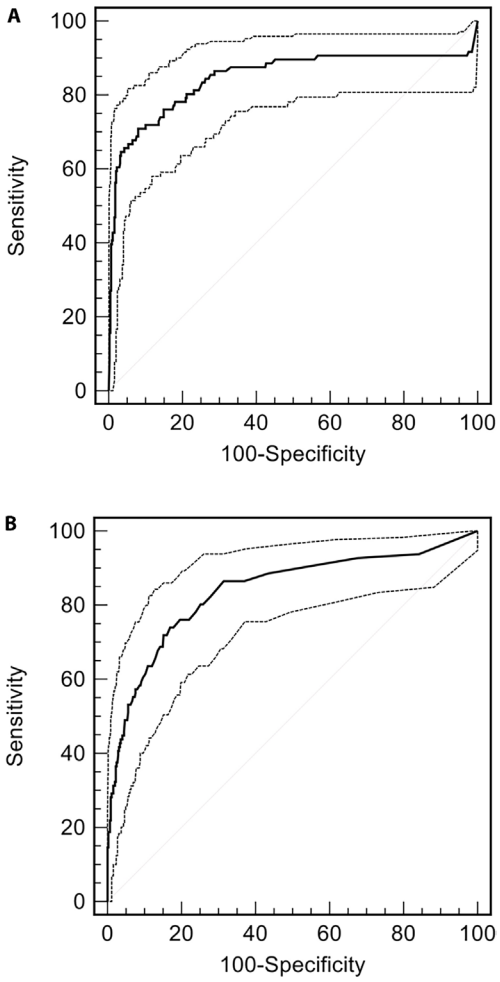

Figure 1. ROC curve of bacteriuria (A) and leukocyturia (B) obtained from the sediMAX-2 results of the training group. Dotted lines represents the 95% confidence bounds.

the ROC curves' derived cutoff 66.3% of the UC could be avoided whereas 2.8% of the urine samples with BAC<228.5 cell/μL and/or WBC<14.5 cell/μL became culture positive. Out of 546 samples only 184 would have been subjected to UC, however, of the remaining 362, 10 individuals, having UTI (according to UC), would have been misdiagnosed.

With the aim of minimizing the number of samples needing UC while maximizing the sensitivity of the sediMAX-2 measurements, we empirically identified two couples of cutoff values based on the training group data. The first BAC/WBC combined cutoff was set using as thresholds 110 and 15 cell/μL for BAC and WBC, respectively, and was called cutoff-A. Based on

cutoff-A only samples showing both BAC>110 cell/μL and WBC>15 cell/μL would be subjected to UC. Cutoff-A was selected in order to achieve the best compromise between sensitivity (97.9%) and specificity (66.0%). The PPV and NPV were 38.1% and 99.3%, respectively (Table 2). Thus 54.8% of the UC could be avoided while only 0.7% of the urine samples with BAC<110 cell/μL and/or WBC<15 cell/μL became culture positive.

The second cutoff (cutoff-B) was empirically developed with the aim of maximizing only the sensitivity. Cutoff B was set using as thresholds 50 and 20 cell/μL for BAC and WBC, respectively.

Thus, only samples showing both BAC>50 cell/μL and WBC>20 cell/μL would be subjected to UC. Cutoff-B yielded a sensitivity and a specificity equal to 99.0% and 40.0%, respectively, whereas the PPV and NPV were 26.0% and 99.4% respectively (Table 2). Thus 33.2% of the UC could be avoided while 0.6% of the urine samples with BAC<50 cell/μL and/or WBC<20 cell/μL became culture positive. By using cutoff-B only one patient having UTI (according to UC) would have been misdiagnosed on the basis of the sediMAX-2 results. Notably, the misdiagnosed patient showed no presence of WBC and had a very low BAC value (6 cell/μL) indicating that UC positivity might have been the consequence of bacterial contamination. Taking the latter into account, the NPV would raise to 100%.

Validation group

Of the 230 samples tested in the validation group, 36 (15.7%) showed positive UC results. The percentage is slightly lower but similar to that observed in the training group (17.6%). The presence of nitrite (6.1%) was similar to the training group and consistent with high specificity and low sensitivity (99.5% and 36.0%, respectively) and with PPV and NPV equal to 93.3% and 89.2%, respectively.

Table 3 shows that by using the manufacturers' suggested cutoff combination (BAC>90 cell/μL and/or WBC>9 cell/μL) the sensitivity was similar to that of the training group (94.4 and 97.9% respectively). By using the manufacturers' suggested combination 35.7% of the UC could be avoided yet, 2.4% of the urine samples with both BAC<90 cell/μL and WBC<9 cell/μL became culture positive. Thus, by applying the manufacturers' cutoff combination, out of 230 samples, two individuals having UTI (according to UC), would have been misdiagnosed based on the sediMAX-2 results.

As observed in the training group, by using the cutoffs combination obtained from the ROC curves (BAC>228.5 cell/μL and/or WBC>14.5 cell/μL), the number of samples sent for UC was rather small (32.2%). However, the NPV was the lowest among the different BAC/WBC cutoff combinations (Table 3), and the number of patients with UTI that would be misdiagnosed based on the sediMAX-2 measurements reached 3.9%.

By using the manually developed cutoff-A (BAC>110 cell/μL and/or WBC>15 cell/μL) the sensitivity (91.7%) and the specificity (53.1%) were slightly lower than those observed in the training group; 46.1% of the UC could be avoided but 2.8% of the

Table 2. Statistical parameters obtained by applying the considered cutoff values to the training group. UC (%) represents the percentage of samples that will be cultured after the sediMAX-2/ Aution Max AX-4030 analysis based on the corresponding cutoff.

Cutoff type		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	UC (%)	Missed UTI (%)
Nitrite	Present/absent	43.8	99.3	93.3	89.2	8.2	7.9
Manufacturer suggested	BAC >90 and/or WBC > 9 cell/μL	97.9	56.2	32.3	99.2	53.3	0.4
ROC curve derived	BAC >228 and/or WBC > 14 cell/μL	89.6	78.2	46.7	97.2	33.7	1.8
Cutoff-A	BAC >110 and WBC > 15 cell/μL	97.9	66.0	38.1	99.3	45.2	0.4
Cutoff-B	BAC >50 and WBC > 20 cell/μL	99.0	40.0	26.0	99.4	66.8	0.2

Table 3. Statistical parameters obtained by applying the considered cutoff values to the validation group. UC (%) represents the percentage of samples that will be cultured after the sediMAX-2/ Aution Max AX-4030 analysis based on the corresponding cutoff.

Cutoff type		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	UC (%)	Missed UTI (%)
Nitrite	Present/absent	36.0	99.5	92.9	89.4	6.1	10.0
Manufacturer suggested	BAC >90 and/or WBC > 9 cell/μL	94.4	41.2	23.0	97.6	64.3	0.9
ROC curve derived	BAC >228 and/or WBC > 14 cell/μL	75.0	75.8	36.5	94.2	32.2	3.9
Cutoff-A	BAC >110 and WBC > 15 cell/μL	91.7	53.1	26.6	97.2	53.9	1.3
Cutoff-B	BAC >50 and WBC > 20 cell/μL	100	27.3	20.3	100	78.0	0

samples with BAC<110 cell/μL or WBC<15 cell/μL would became culture positive.

In contrast, by using cutoff-B (BAC>50 cell/μL and/or WBC>20 cell/μL) both the sensitivity and the NPV reached 100% (Table 3). While avoiding 22.0% of UC, all the patients having UTI (according to UC) could be correctly diagnosed based on sediMAX-2 results.

Discussion

Detecting nitrite, WBC and BAC in urine samples represents a crucial step in the diagnosis of a UTI (24). At the San Raffaele Hospital in Milan, Italy samples are tested with the sediMAX-2/AutionMax-AX-4030 coupled instrumentation. The manufacturer provided specific cutoff values, yet, they were not derived from a population study. Accordingly, the manufacturer does not preclude users from developing and validating their own cutoff values to achieve their desired diagnostic goals (17). In this study, we developed new cutoff values by analyzing a relatively high number of clinical samples. The statistically significance of the sample size analyzed in this study was confirmed by the fact that the percentage of diagnosed UTI, as well as the percentages of the most frequent strains, were very similar to those reported in previous studies (1,23) where more than 7000 samples were examined.

As expected, nitrite showed a very high specificity (>99%). If detected, its presence is particularly helpful to rule in positive culture in UTI. Because of its high specificity, there was no need to combine the presence of nitrate with WBC and/or BAC for a triple combined cutoff.

In contrast, the presence of WBC or BAC is less specific, and a careful combination of their cutoff values was needed to optimize the instrumentation outputs. The cutoff based on the ROC curves' results had the advantage of avoiding the highest percentage of UC (65-70%), yet was associated with the lowest NPV. This cutoff guarantees large money savings but is associated with a relatively high risk of UTI misdiagnosing. By considering that approximately 200 UC are performed, daily, in a medium/large hospital like the San Raffaele Hospital in Milan, and that a single UC costs approximately 15 dollars, avoiding 70% of them represents a yearly savings for the National Health System of approximately 200000 dollars, if compared with the manufacturers' suggested one. Yet, misdiagnosing patients with UTI could lead, in some cases, to legal appeals, which are also very expensive for the hospital.

Cutoff-A, when compared to the manufacturers' suggested one, showed a higher NPV and could avoid a larger number of UC (approximately 10% more) while keeping the misdiagnosis rate essentially the same. In economic terms, cutoff-A allows a net saving (for a medium/large hospital) of approximately 100000 dollars' worth of UC, when compared to the manufacturers' suggested one. Cutoff-B was empirically developed with the aim of minimizing the number of misdiagnosed UC. It showed a NPV of 100% in both groups (if considering the single misdiagnosed sample in

the training group as bacterial contamination). In economic terms, using cutoff-B will represent, for medium/large hospitals, a spending increase of approximately 100000 dollars (when compared to the manufacturers' suggested one), which represents the price to spend to avoid any wrong diagnosis.

We believe that the proposed cutoffs can be implemented by other laboratories, using similar instrumentation, to reach their desired balance between diagnostic and economic needs.

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Ethic Committee: All patients or their legal representatives gave informed consent authorizing the use of their anonymously collected data for the research studies (article 9.2.j of the EU general data protection regulation 2016/679 [GDPR]), according to the San Raffaele Hospital internal policy (IOG075/2016).

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.), in particular with the Menarini company, that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: DF: writing, data analysis; MT: performed the analysis; MV: statistical analysis; ML: data analysis

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