

Risk associated with dipstick urinalysis for diagnosing urinary tract infection

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ABSTRACT

Urinary tract infections (UTIs) are highly prevalent in the Brazilian population. Rapid tests, such as the urinalysis reagent strip and/or microscopy, guide the early diagnosis of UTIs and determine the performance of urine cultures. The objective of this work was to evaluate the sensitivity, specificity and diagnostic accuracy of urinalysis by dipstick tests and compare with microscopic examination and culture and sensitivity of urine.

A total of 400 patients participated in this study, which included medical requests for urinalysis strip reagents, microscopy and urine cultures. Random 50-ml samples were obtained at least two hours after the last urination; midstream urine samples were obtained after the participant had performed personal hygiene.

The specificities were nitrite 99.7%, leukocyte esterase 85.2%, leukocyturia 78.2%, bacteriuria 96.6%, bacterioscopy 96.6%, and urinalysis 63.9%, with sensitivities of 27.9%, 44.2%, 76.7%, 81.4%, 81.4 and 97.7%, respectively; the area under the curve (AUCs) were 0.638, 0.647, 0.774, 0.890, 0.890 and 0.808, respectively, and the urine culture was considered the gold standard. Comparing the bacteriuria and bacterioscopy of all of the studied tests and parameters, the accuracy was below $P < 0.01$.

Keywords: Diagnostic accuracy; reagent strips; urinalysis; urinary tract infections.

Introduction

The urinary tract infections (UTIs) are among the most prevalent infectious diseases in the general population. The estimated incidence is of 18/1.000 people per year, (Grabe et al, 2009), (Bader and Hawboldt, 2010). They are more common in women and are associated with significant mortality and morbidity, (Foxman, 2002), (Hsueh et al, 2011), (Hooton, 2012).

When there are symptoms such as dysuria with acute frequency of urination, low back pain with fever and malaise, the diagnosis of cystitis and acute pyelonephritis is not difficult. However, it becomes more complicated when there are less specified symptoms (Khasriya et al, 2010). Three methods are used to establish a clinical diagnosis of UTI, urine culture by using midstream sample, urinalysis through reagent strip and microscopic examination of freshly harvested urine by the identification of leukocyturia higher than 10 μ L and/or increased bacteriuria, (Gadeholt, 1968), (Latham, 1984). The urinalysis by reagent strips constitutes an indirect method of

assessment of leukocyturia and bacteriuria through the detection of leukocyte esterase and conversion from nitrate to nitrite, respectively.

The high cost and delay normally required to obtain the urine culture results, which is regarded as the reference standard for excluding the diagnosis of UTI, are factors that hinder its use as a diagnostic tool, (Hooton, 2012). Thus, it resulted in the development of different studies in order to develop and evaluate rapid methods that allow excluding and/or validating the UTIs diagnosis.

Some researchers believe that performing urinalysis for nitrite and leukocyte esterases through reagent strips constitute reliable diagnostic tests to the diagnosis of UTIs. They may even result in a reduction of urine cultures performances up to 18% in situations of emergency, (MacGowan et al, 1990), (Joul and Powers, 1998) and symptomatic UTIs diagnosis, (Powell et al, 1987). Other researchers, on the other hand, believe that the tests performed by reagent strips have little diagnostic value,

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(Koss et al, 2006), (Semaniuk and Church 1999). Therefore, the search for faster and affordable alternatives as well as the evaluation of sensitivity, specificity and diagnostic accuracy determined by the area under the curve (AUC) of the receiver operating characteristics (ROC) of the available methodologies, constituted into a continuous process of searching, (Evans et al, 2006), (Guay, 2008), (Little et al, 2009), (Whiting, 2006) .

This study was conducted with patients that attended the outpatient clinic at the University Hospital of the Federal University of Santa Catarina (HU/UFSC). The objective was to evaluate the sensitivity, specificity and diagnostic accuracy of tests for nitrite and leukocyte esterase performed by reagent strips, leukocyturia, bacteriuria and bacterioscopy by Gram staining to guide the diagnosis of UTIs and define the realization of urine culture, considering the examination of urine culture as the gold standard.

Abbreviations

UTIs - Urinary tract infections;

AUC - Area under the curve;

ROC - Receiver operating characteristics;

Methods

Patients and study design

This study was conducted from September to December 2012 with 400 volunteers aged over 18 years old. They had medical request to perform urinalysis by reagent strips, manual microscopy and urine culture. They attended the Clinical Analysis Laboratory at the University Hospital of the Federal University of Santa Catarina.

All of the individuals who participated in this study signed an informed consent form according to the protocol approved by the Ethics Committee on Research with Humans of the Federal University of Santa Catarina (CEPSH/UFSC: 2193/11). The study was conducted with midstream sample urine. It was considered as the gold standard to the diagnosis of urinary tract infection the presence of $>10^5$, more UFC/ml of urine or 10^3 UFC/mL of urine when there was only the growth of *Escherichia coli*, (NCCLS, 2001).

Collection of urine samples

The urine samples were obtained by collecting 50 mL of midstream sample urine after the individuals were informed about the hygiene methodology and sample collection (midstream clean catch method). The first urine stream of a few seconds was discarded, and after that, the samples were collected in a sterile bottle without interrupting the urination. The samples were obtained, at least, two hours after the previous urination.

Urine culture

The urine samples, immediately after harvest, were sown in aerobiosis in agar CLED (Cystine Lactose-Electrolyte-Deficient) using a disposable loop calibrated for 1uL and incubated at 37°C for 24 hours.

Test for detecting nitrite and leukocyte esterase

The tests for the detection of nitrite and leukocyte esterase of urinalysis by reagent strips and manual microscopy were performed within 2 hours after collecting the urine samples, at a temperature of 20°C and using reagent strips ComboStik 11M®. The analysis of the reagent strips was conducted with the spectrophotometer of semi-automated reflectance Plus LabUReader®.

The reagent strips showed sensitivity to the detection of nitrite (11µmol/L) and leukocyte esterase related to 20-25 leukocytes/µL. These variables were dichotomously classified as "negative" when the result was negative or traces, and "positive" when it was positive (+) or more.

Determination of leukocyturia, bacteriuria and bacterioscopy by Gram

The leukocyturia and bacteriuria were determined through the bright field microscopy, and it was performed within 2 hours after collecting the urine samples. In preparation for microscopic analysis, the urine samples were concentrated 20 times (20-fold) by centrifugation of 10 mL of urine, in conical tubes, for 5 minutes at 400 x g, and the obtained sediment was resuspended to 0.5 ml with the supernatant of urine.

After that, it was loaded in a Neubauer chamber (Neubauer chamber hemocytometric counting chamber) and the preparation was analyzed by using 10X ocular and 40X objective (total increase of 400X). The counting was performed by enumerating the leukocytes found in the large square out of the leukocytes count. Thus, the total is divided by two in order to achieve the final result in the number of leukocytes per microlite (µL) of urine.

The leukocyturia was considered positive when the leukocytes count was bigger than 10/µL. In the evaluation of bacteriuria, when it was observed more than 100 bacteria per large square field out, the result was considered positive. The assessment of the number of bacteria, through the stained bacterioscopy by Gram, was performed in all urine samples through non-centrifuged sediment.

Then, approximately two drops of fresh urine specimen were placed under the blade. After they had dried, the staining of Gram through coloring patterns was performed. After the blade had dried, immersion oil was added; so, it was possible to observe in a total increase of 100X, and the observation of one or more bacteria per microscopic field was considered positive.

Statistical Analysis

The area under the receptor operating characteristic curve (ROC), sensitivity and diagnostic specificity to the parameters nitrite, leukocyte esterase, leukocyturia, bacteriuria, urinalysis (combination with one of these results of urinalysis by reagent strips and positive manual microscopy), and bacterioscopy based on staining characteristics by Gram were calculated. When there was a

comparison under the ROC curves of the analyzed parameters, the non-parametric test of De Long was used. A value of $P \leq 0.05$ was considered significant. The statistical analysis was performed by using the statistical program MedCalc® version 12.4.0 (MedCalc Software bvba, Ostend, Belgium).

Results

The values of sensitivity, specificity to the diagnosis of urinary tract infections and the areas under the curves (AUCs) for positive results of the parameters nitrite, leukocyte esterase, leukocyturia, bacteriuria, urinalysis (combination with one of these results of the urinalysis by reagent strips and positive manual microscopy) and bacterioscopy based on coloration characteristics by Gram are shown in Table 1.

Table 1: Sensitivity, specificity and AUCs for the positive results of the nitrite tests, leukocyte esterase and parameters of leukocyturia, bacteriuria, bacterioscopy of Gram stains and for urinalysis in diagnosing UTIs.

Tests and Parameters	Sensitivity	Specificity	AUC	95% IC	P Value
Nitrite	27.9	99.7	0.638	0.589-0.685	0.0001
Leukocyte esterase	44.2	85.2	0.647	0.598 - 0.694	0.0002
Leukocyturia	76.7	78.2	0.774	0.730 - 0.815	0.0001
Bacteriuria	81.4	96.6	0.89	0.855 - 0.919	0.0001
Bacterioscopy by Gram	81.4	96.6	0.89	0.855 - 0.919	0.0001
Urinalysis ^a	97.7	63.9	0.808	0.766 - 0.845	0.0001

CI - confidence interval; AUC, area under the curve.

Urinalysis^a: Routine urinalysis when there is positivity for any of the following parameters: nitrite, leukocyte esterase, leukocyturia and bacteriuria.

Level of significance: $P < 0.05$.

The urinalysis was the variable that presented the highest sensitivity (97.7%). Bacteriuria and bacterioscopy were the isolated parameters that showed the highest sensitivity (81.4%). The positive tests for nitrite (27.9%) and leukocyte esterase (44.2%) presented the lowest sensitivities while leukocyturia showed sensitivity levels of 76.7%.

The nitrite test showed the highest specificity (99.7%). Bacteriuria and bacterioscopy also presented high specificity (96.6%). However, leukocytes esterase and leukocyturia only showed specificities of 85.2% and 78.2%, respectively. Among the parameters studied, the urinalysis presented the lowest specificity (63.9%).

After establishing the diagnostic value of the analyzed parameters and tests, by comparing these results with the ones obtained through the urine culture (Table 2), it was possible to find that nitrite and leukocyte esterase showed the lowest diagnostic accuracies, with AUCs of 0.638 (95% CI: 0.589-0.685) and 0.647 (95% CI: 0.598-0.694), respectively.

While leukocyturia presented the AUC of 0.774, which was lower than the one demonstrated by bacteriuria and bacterioscopy (AUC=0.890), the urinalysis AUC was 0.808 (95% CI: 0.766-0.845). Bacteriuria and bacterioscopy by Gram had better diagnostic value than the other parameters studied; however, the difference of AUCs observed between them was not significant.

The ROC curves of tests and parameters studied, considering the urine culture as the gold standard, are shown in Figure 1. The AUCs of positive results for nitrite tests and leukocyte esterase were lower than the AUCs calculated for bacteriuria and bacterioscopy ($P < 0.0001$). The positive results for

leukocyturia and urinalysis also had lower AUCs than bacteriuria and bacterioscopy. However, when the AUCs were compared for bacteriuria and bacterioscopy, there was no difference between them (Table 2).

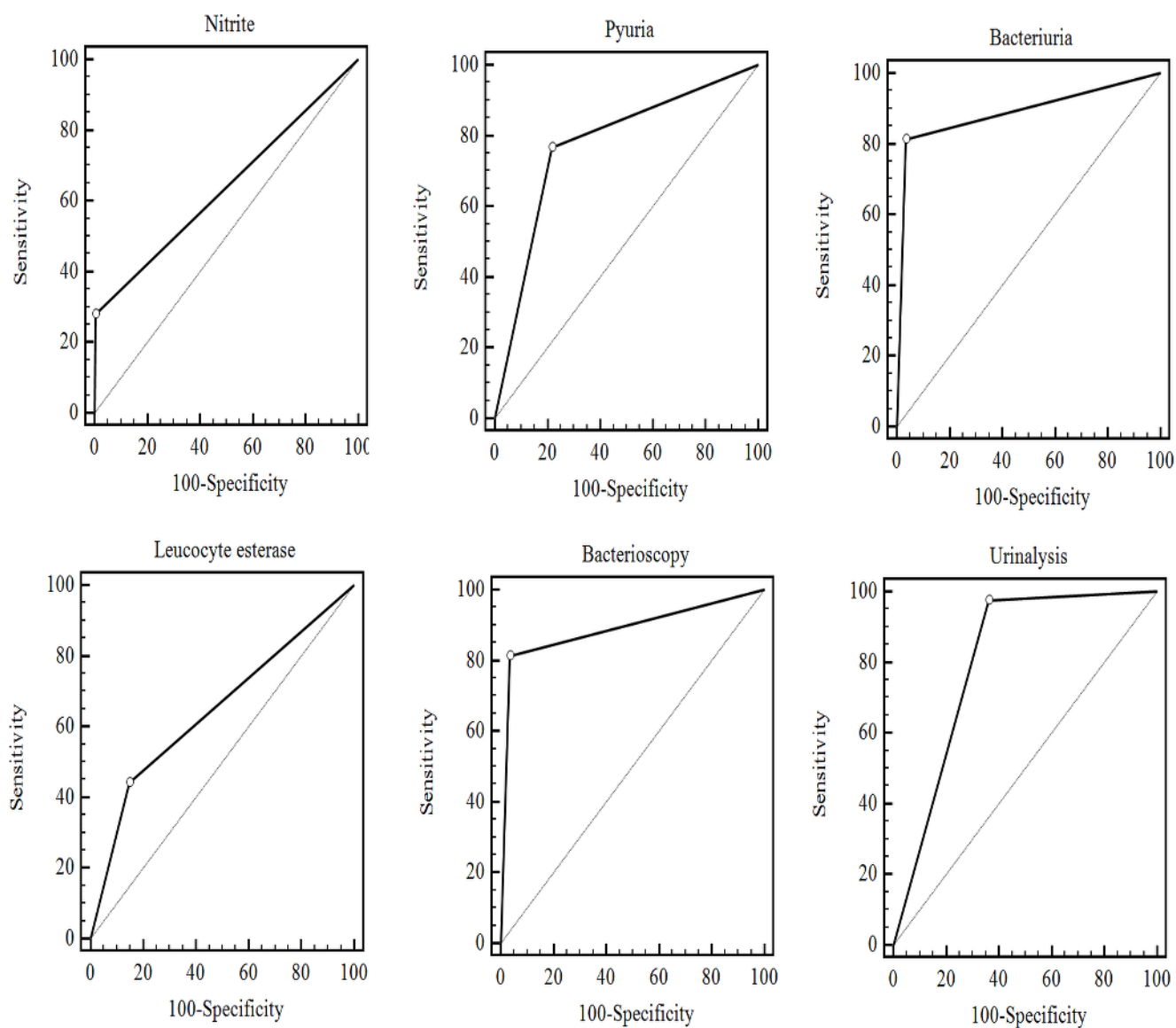


Figure 1: Receiver operating characteristic (ROC) curve with 95% CIs of the nitrite, pyuria, bacteriuria, leucocyte esterase, bacterioscopy and urinalysis parameters.

Table 2: Comparisons of AUCs calculated for the nitrite, leucocyte esterase, leukocyturia and bacterioscopy with bacteriuria parameters.

Comparisons	AUC	95% CI	P value
Nitrite x Bacteriuria	0.638 x 0.647	0.176 - 0.328	0.0001
Leucocyte esterase x Bacteriuria	0.647 x 0.890	0.161 - 0.326	0.0001
Leukocyturia x Bacteriuria	0.774 x 0.890	0.033 - 0.198	0.0061
Urinalysis ^a x Bacteriuria	0.808 x 0.890	0.021 - 0.144	0.0082
Bacterioscopy x Bacteriuria	0.890 x 0.890	0.000 - 0.000	1

CI - confidence interval.

Urinalysis^a: Routine urinalysis when there is positivity for any of the following parameters: nitrite, leucocyte esterase, leukocyturia and bacteriuria.

Level of significance: P<0.05.

Discussion and Conclusions

In this study, the sensitivity, specificity and AUCs from the tests of nitrite and leukocyte esterase by reagent strips, leukocyturia and bacteriuria through microscopy that constitute the urinalysis, bacterioscopy by Gram and urine culture were evaluated in urine samples. Four hundred patients were treated at the outpatient clinic, aged 18 years and above, who presented medical requirements to perform urinalysis and urine culture. Studies performed by several investigators showed that the specificity of tests to detect the nitrite as an indicator of UTIs diagnosis, by reagent strips, may vary from 78.7% to 99.0% while the variation of sensitivity might be from 10.0% to 80.0%, (Khasriya et al, 2010), (Bailey, 1995), (European Confederation of laboratory medicine, 2000), (Bulloch et al, 2000), (Devillé et al, 2004), (Arinzon et al, 2009), (Taneja et al, 2002). The results demonstrate that the nitrite test through reagent strips presented the highest specificity for UTIs diagnosis among the tests and parameters assessed in this study (99.7%), with AUC of 0.638. The high specificity shows that it is necessary to achieve urine cultures whenever the specimen is positive for this test. However, the test for nitrite had the lowest sensitivity (27.9%), which demonstrates that negative results should not be used to rule out the possibility that the urine sample belongs to a patient with UTI. The nitrite detected in urine samples by the reagent strips is produced from the dietetic nitrate that is present through bacteria containing nitrite reductase, like *Escherichia coli*, (Jennifer et al, 2001) and species of *Enterobacter*, *Citrobacter*, *Klebsiella* and *Proteus*, (Oneson and Groschel, 1985). The possibility of a positive test for nitrite is higher when the bacteriuria is greater than 10^5 , (Oneson and Groschel, 1985), (Semeniuk and Church, 1999). (Van Nostrand and colleagues, 2000) showed through their studies that false-negative results may be observed in up to 78.9% of urine samples containing bacteria that reduce nitrate to nitrite. The false-positive results may result from a reduction of nitrate from the diet, dilution of nitrite in the sample caused by the use of diuretics, infection by non-reducing bacteria of nitrite including *Staphylococcus*, *Enterococcus* or *Pseudomonas*, (Pappas, 1991), sample dilution and insufficient incubation time due to the collection of a random sample. Moreover, considering that the minimum limit of nitrite detection by the reagent strips may vary from 11 mmol/L to 13 or 22 mmol/L, (Combostik, 2010), (Combur 10 Test@ UX, 2010), (H-800-Series, 2010), (Multistix @ 10 SG - 2300, 2003), the false-negative results may be due to the lowest detection limit presented by some reagent strips.

The leukocyte esterase is an enzyme found in the neutrophils' granules, and whose number is remarkably low in normal samples $<10\mu\text{L}$. The leukocyte esterase test, according to the performance of various studies may show specificity from 56.0% to 85.0%, and sensitivity from 58.0% to 80.0%, (Khasriya et al, 2010), (Bailey, 1995), (Bulloch et al, 2000), (Taneja et al, 2010), (Lyon et al, 2003), (Thuvo et al, 2010). The results of this study demonstrated specificity of 85.2%, sensitivity of 44.2% with AUC of 0.647.

The leukocyturia had lower specificity (78.2%) than the nitrite and leukocyte esterase; however, the sensitivity was higher than these two tests (76.7%) with AUC of 0.774. Although false-negative results can be verified in tests for leukocyte

esterase, in samples with high specific gravity or containing glucose and/or proteins, (Combur 10 Test@ UX, 2010), (Multistix @ 10 SG - 2300, 2003), they are not quite frequent. Meanwhile, leukocyte esterase, as well as leukocyturia, might be positive in diseases of the urinary tract ranging from urethritis caused by *Chlamydia* or *pyelonephritis* (Jennifer, 2001). Furthermore, the differences observed in this study and others that assessed the sensitivity, specificity and accuracy of leukocyte esterase tests for the diagnosis of UTIs, (Khasriya et al, 2010), (Devillé et al, 2004), (Taneja et al, 2010), must be attributed to the large variation of minimum limits of detection, from 5 to 25 leukocytes/ μL , provided by the reagent strips that can be used in the urinalysis, (Combostik, 2010), (Combur 10 Test@ UX, 2010), (H-800-Series, 2010), (Multistix @ 10 SG - 2300, 2003), (Uriscan, 2007), (Diascreen, 2004).

Still, it must be considered that, in some cases, these values are not even informed by the manufacturer, (Invistrip 10, 2011), (Uri-Color Check, 2010), (SelfStick, no date), (Guilin, no date).

The positive results for bacteriuria, which were observed in this study, showed greater sensitivity and specificity than the one observed by (Bailey and colleagues, 1995), (Bailey, 1995). Although, in almost 25% of the UTIs the number of bacteria is not $\geq 10^5$, according to the description made by (Koeijers and colleagues, 2007), (Koeijers et al, 2007), bacteriuria and bacterioscopy were the isolated parameters that exhibited the highest sensitivity (81.45) and specificity (96.6%) among the studied ones, with AUC of 0.890. The urinalysis by reagent strip and microscopy, considering as a positive result the abnormality of any of the tests and studied parameters, showed a higher sensitivity (97.7%) for the diagnosis of UTI; however, with specificity of only 63.9% and AUC of 0.808. Thus, according to the results of this study, bacteriuria and bacterioscopy are the parameters that exhibit the highest accuracy for the diagnosis of urinary tract infections.

These parameters do not offer diagnostic accuracy enabling to consider the possibility of replacing the urine culture in the diagnosis of UTIs. Nevertheless, they may be considered as the best and fastest screening tests at a low cost that are available to guide early diagnosis of UTIs and set the realization of urine culture.

In conclusion, this study's results allow to state that nitrite and leukocyte esterase tests by reagent strips do not produce any significant sensitivity to be used as the unique markers with the purpose of replacing the urinalysis realization through reagent strips and microscopy to the UTI diagnosis. Also, they might be used as screening tests in order to evaluate the need to request the production of urine culture for UTI diagnosis, and that the use for this purpose represents a considerable risk to the population's health.

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