Archives of Academic Emergency Medicine. 2025; 13(1): e44

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ORIGINAL RESEARCH

Performance of Gram Stain, Leukocyte Esterase, and Nitrite in Predicting the Presence of Urinary Tract Infections: A Diagnostic Accuracy Study

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Received: February 2025; Accepted: March 2025; Published online: 9 April 2025

Abstract: **Introduction:** While urine culture is the gold standard for the urinary tract infection (UTI) diagnosis, delays in results highlight the need for rapid tests. This study aimed to evaluate the accuracy of urine Gram staining, leukocyte esterase, and nitrite in predicting the presence of UTI. **Methods:** A cross-sectional diagnostic accuracy study was conducted on adult patients undergoing urine culture at a high-complexity hospital in northeastern Colombia. The results of Gram staining and urinalysis (nitrite and leukocyte esterase) were compared to urine culture as the gold standard test, and screening performance characteristics were calculated and reported for individual and combined tests. **Results:** A total of 2,123 urine cultures were analyzed, with 49.8% testing positive. Escherichia coli was the most common pathogen (24.7%), and 76.17% of patients received antibiotics, primarily ceftriaxone (38.7%). Gram staining showed 56.9% (95% confidence interval (CI)=54.4 to 59.4) sensitivity and 76.8% (95% CI=72.6 to 80.5) specificity, leukocyte esterase had 67.9% (95% CI= 65.3 to 70.4) sensitivity and 84.5% (95% CI=81.4 to 87.2) specificity, and nitrite demonstrated the highest sensitivity (85.3%, 95% CI=82.0 to 88.2). The combination of Gram staining (+), leukocyte esterase (+), and nitrite (+) achieved 87.6% (95% CI=84.2 to 90.5) sensitivity and 94.6% (95% CI=93.1 to 95.9) negative predictive value (NPV), with the decision tree identifying this combination as having the highest diagnostic utility (positive likelihood ratio (PLR) = 23.77, 95% CI=18.34 to 30.80). **Conclusion:** It seems that, integrating urine Gram staining with leucocyte esterase and nitrite improves UTI diagnosis in high-complexity emergency settings, reducing unnecessary urine cultures and antibiotic use while enhancing resource utilization and mitigating bacterial resistance.

Keywords: Urinary tract infections; Urinalysis; Diagnostic tests, routine; Nitrites; Sensitivity and specificity

Cite this article as: Solorzano C, Camila Rubio M, Licht-Ardila M, et al. Performance of Gram Stain, Leukocyte Esterase, and Nitrite in Predicting the Presence of Urinary Tract Infections: A Diagnostic Accuracy Study. Arch Acad Emerg Med. 2025; 13(1): e44. https://doi.org/10.22037/aaemj.v13i1.2619.

1. Introduction

Urinary tract infection (UTI) is a condition that occurs when microorganisms enter and multiply in the urinary tract, including the kidneys, ureters, bladder, and urethra. Besides, it is a common health concern, ranking as the third most prevalent type of infection after respiratory and gastrointestinal infections. UTIs predominantly affect women and older adults and represent a significant burden on healthcare systems (1, 2). The diagnosis of UTI relies on urine culture, considered the gold standard due to its high accuracy in identifying urinary pathogens (3). However, the time required to obtain results is often substantial, and this diagnostic service is not always immediately available in many clinical settings (4-6).

To address these limitations, rapid tests such as Gram staining and urinalysis are commonly employed. Gram staining is a differential staining technique used to classify bacteria into two main groups: Gram-positive and Gram-negative, based on the structural characteristics of their cell walls. This technique differentiates microorganisms according to their ability to retain the primary stain, providing essential information for their identification and microbiological classification (7). Nonetheless, clinical studies have reported variable sensitivities and specificities for Gram staining and urinalysis, with accuracy rates typically ranging from 60% to 80% for the detection of UTIs (5).

The detection of nitrite in urine is crucial for identifying UTIs, as this compound is produced through the bacterial conversion of nitrate. Although traditional dipstick tests provide semi-quantitative results with limited sensitivity, novel methods, such as a portable colorimeter based on the modified Griess reaction, can detect nitrite concentrations as low as 1.6 μM in artificial urine. This increased sensitivity facilitates the early identification of infections, thereby enhancing

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patient care. Furthermore, its integration with mobile applications enables the continuous monitoring of urinary health (8).

In addition, leukocyte esterase is an enzyme produced by white blood cells and serves as a biomarker for the detection of UTIs, indicating leukocyturia associated with a bacterial inflammatory response. The leukocyte esterase test is included in urine dipstick analysis and provides a rapid and non-invasive method for UTI screening. Its sensitivity ranges from 83% to 96%, and its specificity from 78% to 90% (9). However, factors such as contamination with vaginal secretions or Trichomonas infections can lead to false positives, while elevated protein levels or the presence of vitamin C can cause false negatives. The effectiveness of this test increases when combined with other methods, such as nitrite detection and urine culture, to confirm the diagnosis of UTIs (10). These methods provide preliminary results within a short time frame, facilitating the prompt initiation of treatment when UTI is suspected (11). They are valuable in clinical practice as they help guide the initial management of UTIs, reducing delays and enabling timely treatment (12). In clinical practice, the overuse of urine cultures in cases without clear clinical evidence of UTI has emerged as a concern, often leading to unnecessary treatments and increased healthcare costs. This indiscriminate use of diagnostic resources, coupled with the frequent empirical prescription of antibiotics, exacerbates the growing problem of antimicrobial resistance as a critical public health challenge in modern medicine (13). Addressing this issue requires adherence to evidence-based guidelines that emphasize the judicious use of urine cultures and antibiotics, prioritizing their use only in patients with well-defined clinical indications for UTI (14).

Evaluating and optimizing rapid diagnostic tools that balance accuracy, cost, and accessibility is essential to improving clinical outcomes and mitigating the long-term consequences associated with UTIs. This study aimed to evaluate the diagnostic value of urine Gram staining, urine leukocyte esterase, and urine nitrite in detecting the presence of UTI.

2. Methods

2.1. Study design and setting

This cross-sectional diagnostic accuracy study was conducted to assess the screening performance characteristics of Gram staining, and urine leukocyte esterase and urine nitrite evaluations for diagnosing UTI in comparison to urine culture as the gold standard test. All adult patients who underwent urine culture testing during the period of January to September 2024 in the emergency department of a high-complexity healthcare institution in northeastern Colombia were studied.

The study protocol was approved by the institutional ethics committee (Ethics code: CEI-2024-07461-6). All patient data were anonymized to ensure confidentiality, and the study adhered to the principles outlined in the Declaration of Helsinki.

2.2. Participants

Adult patients (aged ≥18 years) with suspected UTI who underwent at least one diagnostic test for evaluating UTI (gram staining, urine nitrite, urine leukocyte esterase, and urine culture) were included. Cases with incomplete records or contaminated urine cultures were excluded. In cases with more than one urine culture per event, the first requested culture was selected. In pregnant women, both urinalysis parameters and at least one urine culture were considered for evaluation. While antibiotic use may reduce microbiological recovery by up to 20%, this factor was not used as an exclusion criterion. Furthermore, based on a literature review, no sufficient data were found to support a significant negative impact of other medications on urinalysis or urine culture results.

2.3. Data gathering

Patient data were extracted from the institutional electronic health record system, including demographic information, clinical presentation, and results of Gram staining, urine nitrite test, urine leukocyte esterase test, and urine culture. The information used in this study was extracted from the medical records using data engineering techniques, ensuring a structured and systematic collection. Subsequently, these data were supplemented and validated by infectious disease specialists and hospital physicians from the Infectious Diseases Department, who were responsible for data collection and verification, ensuring its accuracy and clinical relevance.

Urine Culture was considered the gold standard for identifying urinary pathogens. Cultures were performed using inoculation on MacConkey Agar and Blood Agar. A culture is considered positive when a single organism is isolated at concentrations ≥105 CFU/mL.

Gram staining was performed on uncentrifuged urine samples to identify bacterial morphology and gram characteristics. The procedure involves the sequential application of crystal violet, Lugol's iodine solution, a decolorizing agent (alcohol or acetone), and safranin.

Urinalysis regarding the detection of nitrite and leukocyte esterase was conducted using the COMBUR 10 Test M by Cobas®. This analysis focuses on detecting nitrite with a detection limit of 0.07 mg/dL and leukocyte esterase with a detection limit of 12–25 LEU/μL. The test demonstrates a high concordance rate with other methods, achieving 99% and 100% agreement for nitrite and leukocyte esterase detection, respectively.

2.4. Statistical analysis

Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as medians with their respective 25th and 75th percentiles according to their distribution. The screening performance characteristics (sensitivity, specificity, positive predictive value

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(PPV), and negative predictive value (NPV), area under the curve (AUC), positive likelihood ratio (PLR), and negative likelihood ratio (NLR)) of Gram staining and leucocyte esterase in urinalysis were calculated using urine culture as the reference standard. In addition, the accuracy of various combinations of the studied diagnostic tests in detecting UTI in comparison with urine culture was evaluated. All estimates were reported with 95% confidence intervals (CIs). The analysis was performed using Stata 17.0.

3. Results

3.1. Baseline characteristics of studied patients

In this study, a total of 2,123 urine culture results from adult patients were analyzed. The majority of urine cultures were performed for women (58.0%), with a median age of 60 (interquartile range (IQR):41-74) years, and most patients were from urban areas (85.1%). On admission, 28.6% of the patients were diagnosed with UTI, while 21.8% presented with diagnoses suggestive of an infectious process. Upon hospital discharge, the diagnosis of UTI was confirmed for 35.9% of cases. Escherichia coli (24.7%), Klebsiella pneumoniae (16.9%), and Enterococcus faecalis (14.3%) were the most prevalent detected microorganisms in urine cultures. 66.7% of the patients were hospitalized. Table 1 summarizes the baseline characteristics of the studied cases. Of the 1,986 urinalyses performed, 48.4% were positive.
Of 2,123 samples, 49.8% showed positive urine cultures, while 50.2% were negative. The percentages of positive test results for urine leukocyte esterase, urine nitrite, and Gram staining were 68.2%, 27.4%, and 76.0%, respectively. Table 2 shows the results of each diagnostic test and their combination.

3.2. Screening performance characteristics of studied tests

Table 3 shows the screening performance characteristics of studied tests in predicting UTI. The area under the receiver operating characteristic (ROC) curve of Gram staining, urine leukocyte esterase, and urine nitrite in predicting the presence of UTI was 0.67 (95% CI: 0.65 to 0.69), 0.76 (95% CI:0.74 to 0.78), and 0.75 (95% CI:0.74 to 0.76), respectively (figure 1). The combination of Gram staining (+), leukocyte esterase (+), and nitrite (+) had a sensitivity of 87.6% (95% CI: 84.2–90.5), specificity of 60.6% (95% CI: 58.3–63.0), NPV of 94.6% (95% CI: 93.1–95.9), PPV of 38.1% (95% CI: 35.2–41.1), PLR of 2.23 (95% CI: 2.08–2.39), NLR of 0.20 (95% CI: 0.16–0.26), and AUC of 0.74 in predicting UTI.

3.3. Decision tree

A decision tree was constructed to evaluate the diagnostic utility of three commonly used tests (Gram staining, leukocyte esterase, and nitrite). Each test was assessed individually, and their likelihood ratios (LRs) were presented at the tree's branches. The final results of the decision tree based on LRs show eight possible combinations. The combination most likely to confirm the disease was found to be positive results for all three tests (Gram staining, Leukocyte esterase, Nitrite), with a cumulative PLR of 23.77 and NLR of 0.05 (Figure 2).

4. Discussion

Numerous negative effects have been associated with the lack of precision in diagnosing UTIs. These include inaccurate diagnoses, unnecessary exposure to antibiotics, adverse effects from antibiotic use (e.g., Clostridioides difficile infection), inappropriate hospital stays, and increased healthcare costs (15). Therefore, it is crucial to evaluate strategies that can reduce unnecessary urine culture testing (16). In this study, we assessed the effectiveness of combining urine Gram staining with urinalysis parameters to detect UTI and to determine when a urine culture should be processed for the diagnosis of UTI.
In Northern Denmark, Kristensen et al. evaluated the performance of combining leukocyte esterase and nitrite (positive results for either or both) and reported a sensitivity of 87% and a specificity of 45%, with a PLR of 1.58 and an NLR of 0.30. Using pretest probabilities based on centers for disease control and prevention (CDC) definitions (28% for costovertebral pain and 60% for dysuria), they estimated that the post-test probabilities increased to 35% (95% CI: 21% to 50%) and 68% (95% CI: 55% to 80%) in patients with a positive dipstick test for leukocyte esterase, nitrite, or both. Conversely, the post-test probabilities decreased to 12% (95% CI: 1% to 36%) and 27% (95% CI: 8% to 55%) in patients with a negative dipstick test (17).
Our findings support the utility of negative leukocyte esterase and nitrite in ruling out a UTI diagnosis. However, positive results for these markers alone cannot definitively confirm UTI due to their limited post-test probability. Importantly, the study by Kristensen et al. did not incorporate urine Gram staining in their analysis. In contrast, our study demonstrated an improved positive PLR of 9.7 and an NLR of 0.06 for the combination of leukocyte esterase and nitrite, offering greater discriminative power. Furthermore, we included urine Gram staining in our analysis, enhancing the diagnostic framework.
A 2013 study conducted on 212 pregnant women in Colombia evaluated urinalysis, urine Gram staining, and nitrite. The urinalysis criteria for positivity included >5 leukocytes/high-power field, >5 red blood cells, or >2+ bacteria. Urine Gram staining achieved a sensitivity of 74% and specificity of 86%, while urinalysis had a sensitivity of 21% and specificity of 92%. Nitrite showed a sensitivity of 30% and a specificity of 97% (14). Although that study assessed the accuracy of combining urine Gram staining and urinalysis, its PLR values were not superior to those of urinalysis components alone, despite higher sensitivity for Gram staining (18).
Our results confirm that neither urine Gram staining nor urinalysis alone is sufficient to reliably rule out UTI or predict a

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negative urine culture.
This study was conducted in a high-complexity healthcare institution, focusing on patients presenting to the emergency department. The implementation of rapid diagnostic tools in such settings has been shown to enhance patient care by reducing diagnostic and treatment times, thereby improving overall clinical outcomes (5). Our findings align with this evidence, suggesting that integrating urine Gram staining with urinalysis parameters can expedite the diagnostic process for UTI in the emergency department. This approach has the potential to optimize resource utilization and reduce unnecessary antibiotic exposure, which is particularly beneficial in high-acuity environments where timely decision-making is critical.
A diagnostic accuracy study conducted in the Netherlands in 2024, based on 718 samples, highlighted the overestimation of UTI diagnoses and antibiotic exposure when relying solely on dipstick tests in pregnant women without infection. This underscores the potential risks of relying exclusively on urinalysis variables for clinical decision-making (19). Our study's findings lie in the combined performance of diagnostic tests in two specific scenarios. First, negative results for urine Gram staining, leukocyte esterase, and nitrite produced an NLR of <0.05, effectively ruling out UTI. Conversely, when all tests were positive, the PLR reached 23.7, strongly supporting a UTI diagnosis. However, other test combinations yielded indeterminate results, necessitating urine culture for confirmation or exclusion.
Despite several studies exploring the costs associated with rapid diagnostics and antimicrobial treatments for UTI (20), none have comprehensively estimated the direct costs of diagnostic tools (e.g., urinalysis, Gram staining, urine cultures) or the indirect costs, including hospital stays, antibiotic use, and adverse effects related to overdiagnosis. A 2014 study in Maryland, USA, focused on processing urine cultures only in cases with pyuria, reducing culture volume by 10% and decreasing catheter-associated UTI (21). However, limited evidence exists regarding the long-term effectiveness and safety of such approaches.
Additionally, a systematic review of pediatric studies proposed a diagnostic algorithm incorporating clinical indicators, leukocyte esterase and nitrite, but the evidence was insufficient to fully validate its utility (22). Pallin et al. (2014) reported that unnecessary antibiotic use in asymptomatic bacteriuria occurred in 28% of cases (23). Applying this figure to our patient population would translate to 594 inappropriate urine cultures, with an estimated cost of $6,058, excluding indirect costs. Thus, implementing a diagnostic optimization strategy could significantly reduce operational costs and align with findings from a 2024 meta-analysis, which highlighted the economic burden of community-acquired UTIs caused by resistant microorganisms.
This study stands out for incorporating urine Gram staining alongside leukocyte esterase and nitrite in a large and diverse patient cohort, making it one of the most comprehensive analyses conducted in Colombia and internationally. The results demonstrate the potential to significantly enhance diagnostic accuracy, reduce unnecessary urine cultures, and lower costs in resource-limited settings. By minimizing inappropriate antibiotic use, these findings also contribute to mitigating bacterial resistance. Future research focusing on specific subgroups of urinary infections could further refine diagnostic strategies and provide tailored insights for improved clinical decision-making.

5. Limitations

While this study provides valuable insights, certain aspects should be considered when interpreting the findings. The retrospective nature of the analysis, along with its focus on a single healthcare institution, may reflect contextual factors specific to the study setting. Additionally, the diverse cohort analyzed does not encompass all possible subgroups, such as patients with recurrent UTI or specific comorbidities, which could influence diagnostic outcomes. These factors, while inherent to the study design, do not diminish the robustness of the results but rather highlight areas for future research to expand and validate these findings in broader contexts.

6. Conclusions

It seems that integrating urine Gram staining with leucocyte esterase and nitrite improves UTI diagnosis in high-complexity emergency settings, reducing unnecessary urine cultures and antibiotic use, while enhancing resource utilization and mitigating bacterial resistance.

7. Declarations

7.1. Acknowledgments

We would like to thank Dr. Anderson Bermon and Alejandra Mendoza-Monsalve for their continuous support and guidance throughout the development of this work. Their collaboration has been essential to its completion.

7.2. Author Contribution

The manuscript has been read and approved by all authors and has not been published and is not currently under consideration for publication elsewhere.
Carlos Solorzano: has participated in the conception and design, analysis and interpretation of data, writing, and revision of the manuscript. María Camila Rubio: has participated in the writing, and revision of the manuscript.
Maricel Licht-Ardila: has participated in the conception and design, analysis and interpretation of data, writing, and revision of the manuscript. Camila Castillo: has participated in the writing and revision of the manuscript.
Juan Camilo Valencia Silva: has participated in the database construction and revision of the manuscript.
María Alejandra Caro: has participated in the writing and revision of the manuscript.

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Edgar Fabián Manrique-Hernández: has participated in the conception and design, analysis and interpretation of data, writing, and revision of the manuscript.
Alexandra Hurtado-Ortiz: has participated in the conception and design, analysis and interpretation of data, writing, and revision of the manuscript.
Liliana Torcoroma García: providing expert advice, assisting in the writing process, and conducting the final revision.

7.3. Conflicts of Interest

The authors declare no financial conflicts of interest or personal relationships that may have influenced the work presented in this article.

7.4. Funding

None to report.

7.5. Data availability

Authors guarantee that data of the study are available and will be provided if anyone needs them.

7.6. Using artificial intelligence chatbots

This article has been created without the use of artificial intelligence. All the information presented and content generated have been developed based on research and prior knowledge.

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Table 1: Baseline characteristics of studied cases

Variables	Values	Variables	Values
Sex		**Age (year)**	
Female	1,232 (58.0)	Median (IQR)	60 (41-74)
Male	891 (41.9)	**Microorganism**	
Health insurance		Escherichia coli	19 (24.7)
Contributory/Special/Specific	1,284 (50.5)	Klebsiella pneumoniae	13 (16.9)
Subsidized	839 (39.5)	Enterococcus faecalis	11 (14.3)
Residence area		Proteus mirabilis	6 (7.79)
Rural	316 (14.9)	Staphylococcus aureus	5 (6.49)
Urban	1,807 (85.1)	Pseudomonas aeruginosa	4 (5.19)
Admission diagnosis		Serratia marcescens	3 (3.90)
Urinary tract infection	608 (28.6)	Staphylococcus saprophyticus	3 (3.90)
Suggestive of infectious process	463 (21.8)	Candida albicans	2 (2.60)
Other Diagnoses	1,052 (49.6)	Enterococcus faecium	2 (2.60)
Discharge diagnosis		Others	11 (14.3)
Urinary tract infection	761 (35.9)	**Urology procedure**	
Suggestive of infectious process	252 (11.9)	No	2,030 (95.6)
Other Diagnoses	1,110 (51.9)	Yes	93 (4.38)
First administered antibiotic		**Non-urology procedures**	
Ceftriaxone	626 (38.7)	No	1,859 (87.6)
Piperacillin/Tazobactam	358 (22.1)	Yes	264 (12.4)
Cefazolin	190 (11.8)	**Hospitalization**	
Meropenem	130 (8.04)	No	707 (33.3)
Ampicillin + Sulbactam	104 (6.43)	Yes	1,416 (66.7)
Other	209 (12.9)		

Data are presented as number (%) or median (inter quartile range (IQR) 25-percentile 75).

Table 2: The results of studied diagnostic tests and their combination

Diagnostic test	Number (%)
Urine Culture	
Negative	1,066 (50.2)
Positive	1,057 (49.8)
Urine leukocyte esterases	
Negative	631 (31.8)
Positive	1,355 (68.2)
Gram Staining	
Negative	487 (24.0)
Positive	1,542 (76.0)
Urine nitrite	
Negative	1,442 (72.6)
Positive	544 (27.4)
Combinations	
Gram Stain (+) Esterases (+) Nitrite (+)	460 (21.7)
Gram Stain (+) Esterases (+) Nitrite (-)	628 (29.6)
Gram Stain (+) Esterases (-) Nitrite (+)	24 (1.13)
Gram Stain (+) Esterases (-) Nitrite (-)	323 (15.2)
Gram Stain (-) Esterases (+) Nitrite (+)	40 (1.88)
Gram Stain (-) Esterases (+) Nitrite (-)	171 (8.05)
Gram Stain (-) Esterases (-) Nitrite (+)	2 (0.09)
Gram Stain (-) Esterases (-) Nitrite (-)	251(11.8)

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Table 3: Screening performance characteristics of gram Staining (GS), urine leukocyte esterase (ULE), and urine nitrite (UN) compared to urine culture as the Gold Standard for detecting urinary tract infections

Test	Sen	Spec	PPV	NPV	PLR	NLR	AUC
GS	56.9 (54.4–59.4)	76.8 (72.6–80.5)	88.6 (86.5–90.5)	36.0 (33.1–39.0)	2.45 (2.08–2.90)	0.56 (0.52–0.60)	0.67
ULE	67.9 (65.3–70.4)	84.5 (81.4–87.2)	90.4 (88.4–92.1)	55.1 (51.9–58.2)	4.37 (3.63–5.25)	0.38 (0.35–0.41)	0.78
UN	85.3 (82.0–88.2)	61.6 (59.0–64.1)	45.6 (42.5–48.7)	91.7 (89.8–93.4)	2.22 (2.06–2.39)	0.24 (0.19–0.29)	0.75
All three	87.6 (84.2–90.5)	60.6 (58.3–63.0)	38.1 (35.2–41.1)	94.6 (93.1–95.9)	2.23 (2.08–2.39)	0.20 (0.16–0.26)	0.74

Sen: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative predictive value, PLR: positive likelihood ratio, NLR: negative likelihood ratio, AUC: area under the receiver operating characteristic curve.

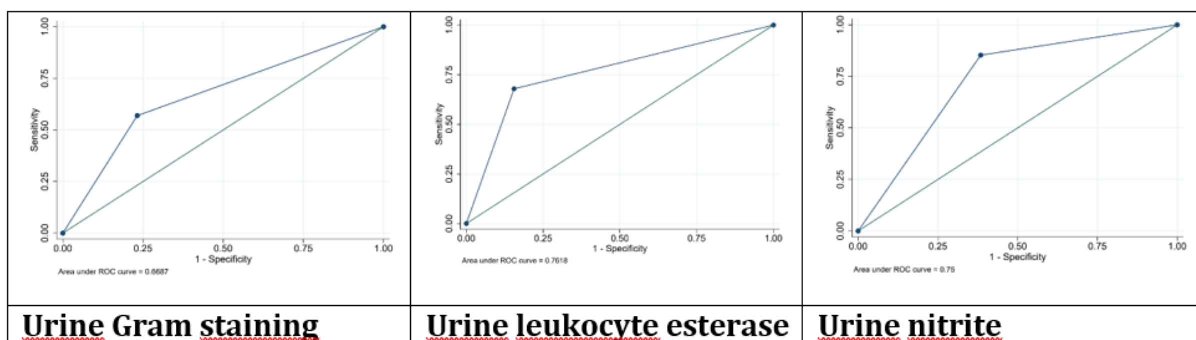

Figure 1: Area under the receiver operating characteristic (ROC) curve of the three studied tests in predicting the presence of urinary tract infection.

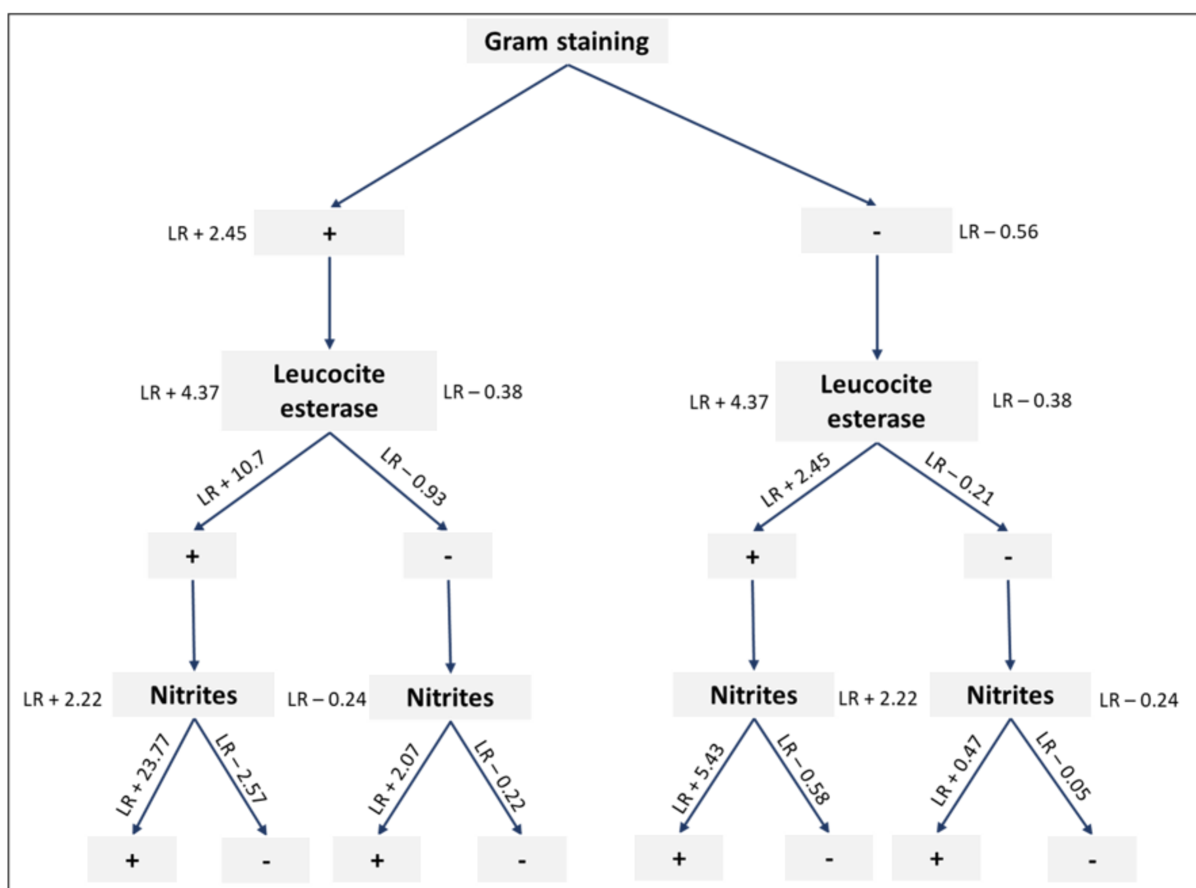

Figure 2: Decision tree for evaluating the diagnostic utility of the three tests. Decision tree illustrating the diagnostic utility of Gram staining, leukocyte esterase, and nitrite for evaluating suspected urinary tract infections. Likelihood ratios (LRs) adjacent to the test boxes represent individual test performance, while LRs along the connecting lines indicate the combined diagnostic performance of sequential tests.

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