# Optimizing urinary tract infection diagnosis: time and resource efficiency with the Sysmex UF-4000i

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## Summary

**Background:** Urinary Tract Infections (UTIs) are common bacterial infections, primarily caused by Gram-negative bacteria, such as *Escherichia coli*. They affect approximately 150 million individuals worldwide annually, leading to high healthcare costs and significant morbidity. The standard diagnostic method, urine culture, has a turnaround time of 48-72 hours, often necessitating empirical antibiotic treatment, which may contribute to antibiotic resistance. Rapid, accurate diagnostic tools are essential to improve clinical microbiology practices.

**Materials and Methods**: this study evaluated the diagnostic accuracy of the Sysmex UF4000i flow cytometer for UTI detection, using traditional microscopy as the reference standard. Conducted over eight months at the Institut Pasteur, Dakar, it involved 2,322 urine samples analyzed via cytological examination and flow cytometry within two hours of collection. Bacterial cultures were performed on Chromagar Orientation media. Diagnostic performance was assessed using Receiver Operating Characteristic (ROC) curve analysis to establish a bacteriuria threshold for excluding UTIs.

**Results:** among the 2,322 samples, bacteriuria was detected in 16.3%, with *E. coli* accounting for 60.7% of positive cultures. The Sysmex UF4000i showed high diagnostic accuracy, with an ROC Area Under the Curve (AUC) of 0.936. A cut-off of 9.85 bacteria/µL achieved a sensitivity of 99.1% and specificity of 53.2%, allowing for the exclusion of 44.9% of samples with a negative predictive value of 99.7%. Performance was consistent across subgroups, including children and women.

**Conclusions:** the Sysmex UF4000i flow cytometer provides a rapid and reliable method for UTI screening, potentially reducing the need for manual urine cultures and minimizing antibiotic overuse while maintaining accuracy.

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## Introduction

Urinary Tract Infections (UTIs) are among the most common bacterial infections worldwide, characterized by the presence of pathogenic microorganisms in the urinary tract, leading to bacteriuria. The infection may involve various parts of the urinary tract, including the urethra (urethritis), bladder (cystitis), or kidneys (pyelonephritis). UTIs primarily affect women and can cause significant morbidity, with millions of cases reported annually. It is estimated that 150 million people are affected globally each year, resulting in considerable healthcare [2]. The predominant causative agents of UTIs are Gram-negative bacteria, especially *Escherichia coli*, followed by other members of the Enterobacteriaceae family. Gram-positive bacteria and yeasts can also cause UTIs, albeit less frequently [3].

Traditional urine culture remains the gold standard for diagnosing UTIs; however, this method is time-consuming, taking 48 to 72 hours for culture and antimicrobial susceptibility testing. This delay can lead to empirical antibiotic treatment, which may contribute to

antibiotic resistance due to inappropriate use. Moreover, up to 70% of urine samples submitted for culture in clinical laboratories do not yield significant bacterial growth [1]. Consequently, there is a need for rapid and accurate diagnostic techniques to reduce turnaround times and enable prompt patient management.

Advancements in automated technologies, such as flow cytometry, offer promising alternatives for rapid UTI screening. The Sysmex UF4000i, a third-generation automated urine analyzer, uses fluorescence flow cytometry to identify and quantify urine particles, including bacteria and leukocytes. This study aims to evaluate the microbiological performance of the Sysmex UF4000i by comparing its results to the gold-standard microscopic examination and determining a bacteriuria threshold below which UTI can be ruled out.

## Materials and Methods

### Study design

This observational diagnostic study was conducted over an eight-month period, from October 2019 to May 2020, at the clinical biology laboratory of the Institut Pasteur, Dakar.

### Sample collection

A total of 2,322 urine samples were collected from routine clinical submissions, including both pediatric and adult patients. Samples were analyzed using both the Sysmex UF4000i and traditional microscopy within two hours of collection. The Sysmex results were blinded to the microscopists to ensure unbiased comparisons.

### Microscopic examination

Urine microscopy was performed using a Kova cell, a disposable device for non-centrifuged urine analysis. Leukocytes and red blood cells were counted manually using a threshold of ≥10 cells/µL for positivity.

### Bacterial culture

Urine culture was performed on Chromagar Orientation agar (Becton Dickinson), a chromogenic non-selective medium that allows direct differentiation and enumeration of urinary pathogens. A 0.01 mL aliquot of well-mixed, non-centrifuged urine was plated and incubated aerobically at 35-37°C for 20-24 hours. Colony counts were interpreted according to Kass' criteria (≥$10^3$ CFU/mL).

### Automated analysis with Sysmex UF4000i

The Sysmex UF4000i employs fluorescence flow cytometry, which measures Forward-Scattered Light (FSC), Side-Scattered Light (SSC), Side Fluorescence (SFL), and Depolarized Side Scatter (DSS) to classify particles. It provides rapid bacterial counts (bacteriuria) and leukocyte counts (leukocyturia) that could potentially guide early UTI management.

### Statistical analysis

Data were processed using R software version 4.1.2. Descriptive statistics were presented as means with standard deviations or medians with ranges for continuous variables and percentages for categorical variables. Receiver Operating Characteristic (ROC) curves were used to assess the diagnostic accuracy of the Sysmex UF4000i, with the Area Under the Curve (AUC) serving as a measure of performance. Cut-off values for bacteriuria were determined using the Youden index, favoring high sensitivity to minimize false negatives.

## Results

### Demographics and sample characteristics

The study population had a median age of 45 years (range: 0-99), with 53% female representation. Children (0-15 years) constituted 10.1% of the cohort. Among the urine samples, 67.3% were clear, while the remainder showed varying degrees of turbidity or hematuria.

### Microscopy and culture findings

Microscopy revealed leukocyturia in 39.5% of samples (≥10□ cells/mL), while bacterial culture confirmed UTI in 16.3% (367/2,322) of cases, predominantly caused by Gram-negative bacteria (91.8%). The most frequently isolated pathogen was *Escherichia coli* (60.7%), followed by *Klebsiella pneumoniae* (15.8%) and *Pseudomonas aeruginosa* (9.5%) (Table 1).

### Sysmex UF4000i performance

ROC analysis demonstrated excellent performance of the Sysmex UF4000i in detecting bacteriuria, with an AUC of 0.936 (95% CI: 0.923–0.950). The optimal bacteriuria threshold was 140.6 bacteria/µL, corresponding to a sensitivity of 86.2% and specificity of 85.4%. To maximize Negative Predictive Value (NPV), a lower threshold of 9.85 bacteria/µL achieved 99.1% sensitivity and 53.2% specificity, effectively ruling out UTI in 44.9% of cases with only a 0.3% false-negative rate (Figure 1).

### Age-specific and gender-specific analysis

For pediatric patients, an AUC of 0.904 (95% CI: 0.854–0.954) was observed, with a cut-off of 54.2 bacteria/µL yielding a sensitivity of 76.9% and specificity of 87.8%. Among female patients, using a 9.85 bacteria/µL cut-off, 27.9% of cases were ruled out with a false-negative rate of 0.2% (Figure 2).

## Discussion

The findings of this study indicate that the Sysmex UF4000i is a highly effective tool for the rapid screening of UTIs, demonstrating a high degree of diagnostic accuracy in detecting bacteriuria. The

**Table 1.** Distribution of microorganisms by traditional urine culture.

| Micro-organisms | N (%) |
|---|---|
| *Escherichia coli* | 221 (60.2) |
| *Klebsiella pneumoniae* | 58 (15.8) |
| *Pseudomonas aeruginosa* | 35 (9.5) |
| *Citrobacter freundii* | 7 (2.0) |
| *Citrobacter koseri* | 3 (0.8) |
| *Acinetobacter baumanii* | 6 (1.6) |
| *Enterococcus* spp. | 12 (3.2) |
| *Staphylococcus aureus* | 12 (3.2) |
| *Streptococcus agalactiae* | 6 (1.6) |
| Other bacteria | 7 (2.0) |

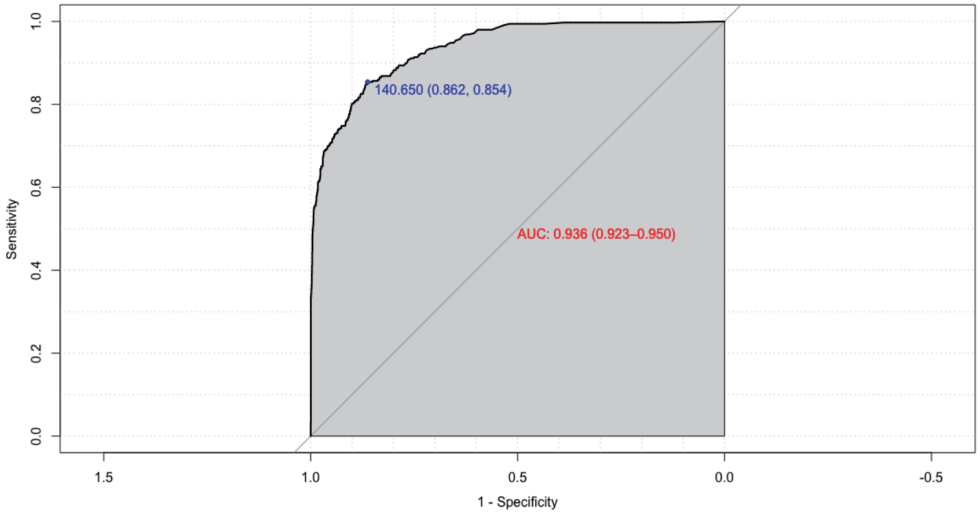


**Figure 1.** Receiver Operating Characteristics (ROC) curve for UF4000 bacteriuria versus culture in all patients (cut-off based on Youden index).

application of fluorescence flow cytometry in urine analysis has shown considerable advantages over traditional methods, including time efficiency, high throughput, and the ability to perform simultaneous quantification of multiple parameters, such as bacteria, leukocytes, and epithelial cells.

Urine culture remains the gold standard for diagnosing UTIs, providing definitive results for bacterial identification and antimicrobial susceptibility testing. However, it is labor-intensive and requires a turnaround time of 24-72 hours, which may delay the initiation of targeted antibiotic therapy [9]. In this context, rapid screening methods are valuable for excluding UTIs in low-risk patients and prioritizing samples for culture based on preliminary results.

The Sysmex UF4000i, as shown in this study, achieved an AUC of 0.936, indicating excellent discriminatory ability. This is consistent with other studies evaluating the performance of automated urine analyzers, which have reported similar AUC values ranging from 0.88 to 0.95 [5,11]. The present study's sensitivity and specificity at the optimal cut-off of 140.6 bacteria/µL (86.2% and 85.4%, respectively) align with these previous findings, further validating the Sysmex UF4000i's utility as a screening tool.

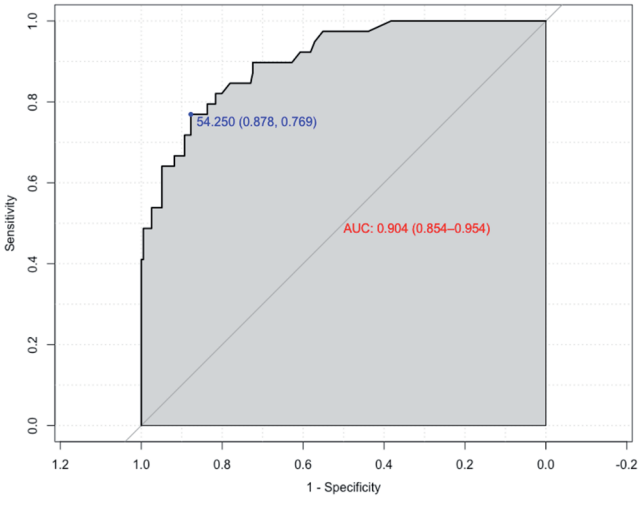


**Figure 2.** Receiver Operating Characteristics (ROC) curve for UF4000 bacteriuria compared with culture in children.

Determining an appropriate bacteriuria threshold is crucial for optimizing the balance between sensitivity and specificity. In this study, a lower cut-off of 9.85 bacteria/µL was chosen to maximize the NPV, achieving a sensitivity of 99.1%, which would allow the exclusion of UTI in 44.9% of cases with a minimal false-negative rate of 0.3%. This threshold ensures that most true cases of UTI are identified, reducing the likelihood of untreated infections. However, using such a low threshold also results in lower specificity (53.2%), potentially leading to higher false positives [5].

In contrast, a higher cut-off may be suitable in settings where it is important to reduce the number of false positives and laboratory workload. For instance, thresholds ranging from 100 to 500 bacteria/µL have been suggested in various studies, with sensitivities around 85-90% and specificities over 80% [5,10]. The choice of threshold may thus be adapted to the clinical context, such as pediatric *versus* adult populations or male *versus* female patients, to account for differences in pre-test probability and contamination rates.

The study also evaluated the performance of the Sysmex UF4000i across different age groups and genders. Pediatric patients often present unique challenges in UTI diagnosis due to the higher likelihood of contamination and non-specific symptoms. In this study, the analyzer demonstrated good performance in children, with an AUC of 0.904 and a sensitivity of 76.9% at a lower cut-off of 54.2 bacteria/µL. This finding is comparable to previous studies in pediatric populations that reported AUC values ranging from 0.85 to 0.92 for various automated urine analyzers [8,13].

The gender-specific analysis showed that using a threshold of 9.85 bacteria/µL in female patients effectively ruled out UTI in 27.9% of cases, with a false-negative rate of 0.2%. Given that women are more prone to UTIs due to anatomical factors, a low threshold for exclusion can be particularly useful for reducing unnecessary antibiotic use in this population, thereby combating antimicrobial resistance.

The Sysmex UF4000i's performance compares favorably with other rapid diagnostic techniques, such as bioluminescence, tur-

bidimetry, and Matrix-Assisted Laser Desorption/Ionization-Time of Flight (MALDI-TOF) mass spectrometry. Bioluminescence assays, which measure bacterial ATP, have shown sensitivities between 70% and 90%, but their specificity tends to be lower than that of flow cytometry-based methods [12]. Turbidimetry, which detects changes in light transmission due to bacterial growth, also offers rapid results but suffers from limited sensitivity, particularly in low bacterial loads [6].

In contrast, MALDI-TOF mass spectrometry can provide highly accurate identification of urinary pathogens within a few hours, especially when coupled with an enrichment step. However, it requires sophisticated equipment and skilled personnel, which may not be available in all laboratory settings [7]. The Sysmex UF4000i, with its fluorescence flow cytometry-based approach, offers a more accessible and user-friendly alternative while maintaining high diagnostic accuracy.

The findings from this study suggest that the Sysmex UF4000i can serve as an effective UTI screening tool, reducing the need for routine urine culture by ruling out infection in nearly half of the samples submitted for testing. This reduction in unnecessary cultures can decrease laboratory workload, cut down costs, and minimize patient exposure to antibiotics. Early identification of bacteriuria may also help to rapidly initiate appropriate antimicrobial therapy, potentially improving patient outcomes [1].

Moreover, the high NPV achieved with a low bacteriuria threshold supports its use as a rule-out test, particularly in settings where empirical antibiotic therapy is common due to diagnostic delays. By accurately identifying negative cases, the Sysmex UF4000i can prevent unwarranted antibiotic prescriptions, thus contributing to antimicrobial stewardship efforts.

While the Sysmex UF4000i shows promise as a screening tool, its performance may vary based on sample quality, patient population, and local epidemiology of UTI pathogens. False positives may occur in the presence of non-bacterial particles such as yeast, which may not always be distinguished from bacteria by fluorescence flow cytometry. Further studies could explore combining flow cytometry with other diagnostic modalities, such as rapid molecular techniques, to enhance specificity.

Future research should also consider evaluating the cost-effectiveness of implementing the Sysmex UF4000i in various healthcare settings, particularly in resource-limited regions where access to comprehensive diagnostic services is limited. Additionally, examining the impact of such automated screening tools on long-term antibiotic usage patterns and resistance trends would provide valuable insights into their role in global antimicrobial resistance management.

Nonetheless, some limitations should be noted. The single-center design may limit the generalizability of the findings to other healthcare settings. Additionally, the performance of flow cytometry in detecting less common pathogens, such as Gram-positive bacteria or fungi, was not evaluated in this study. Future multicenter studies are needed to validate these findings and explore adjustments to the bacteriuria threshold based on local epidemiology and specific patient populations.

## Conclusions

The study demonstrates that the Sysmex UF4000i is a valuable tool for the rapid screening of UTIs. Its high sensitivity and negative predictive value make it especially useful for ruling out UTIs, potentially reducing the need for routine urine cultures and enabling more efficient management of laboratory resources. The flexibility in setting bacteriuria thresholds allows the analyzer to be tailored to specific clinical contexts, such as pediatric or adult populations.

The implementation of the Sysmex UF4000i could facilitate faster decision-making in UTI diagnosis, minimize unnecessary antibiotic use, and contribute to antimicrobial stewardship efforts. However, further studies are warranted to explore its performance across diverse patient groups and healthcare settings, and to integrate it with other diagnostic approaches for enhanced specificity. Overall, the Sysmex UF4000i offers a promising alternative to traditional urine culture, balancing diagnostic accuracy with time efficiency, and addressing the growing need for rapid diagnostic tools in the fight against antimicrobial resistance.

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