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Urine flow cytometry in older adults urinary tract infection diagnosis: is it time to reevaluate thresholds for men and women?

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Abstract

Background To evaluate the utility of automated urine flow cytometry in the diagnosis of urinary tract infection (UTI) in older patients without waiting for urine culture results.

Methods This prospective study included patients aged ≥ 65 years admitted to the emergency department of Besançon University Hospital over a six-month period. Clinical and biological data were collected and UTI diagnosis was based on strict clinical and biological criteria. Urine analysis was performed using the UF-4000 (Sysmex). Parameters or thresholds were defined based on an AUC > 0.8 and a clinically relevant negative likelihood ratio (LR-) < 0.1.

Results Of 456 patients, 69 (15.1%) had a UTI. Bacteriuria (AUC = 0.874) and leukocyturia (AUC = 0.925) were strongly associated with UTI, with thresholds of 150 bacteria/μL and 50 leukocytes/μL (both LR- < 0.1). These cut-offs varied by sex. Urine dipsticks effectively excluded UTI in men (LR- < 0.1), but were less reliable in women (LR- = 0.129). Gender-specific diagnostic algorithms were suggested.

Conclusions Urine flow cytometry provides valuable diagnostic thresholds for bacteriuria and leukocyturia and helps to exclude UTI before culture results. Recommendations for the diagnosis of UTI in older patients should take into account gender differences.

Keywords Urinary tract infection, Elderly, Diagnosis, Flow cytometry, Urine culture

Introduction

Urinary tract infection (UTI) is common and is classically described as urinary symptoms associated with a positive urine culture. Symptoms of UTI can vary widely but often include dysuria, increased frequency, urgency of urination, and lower abdominal pain [1]. However the diagnosis of UTI in older adults is challenging due to atypical or subtle symptoms and frequent cognitive impairment [2]. In addition, urine cultures are often positive due to the high rate of asymptomatic bacteriuria, further complicating the diagnosis [3]. Urine dipsticks, commonly used as a preliminary diagnostic tool, provide

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a rapid and non-invasive method of testing for UTIs by detecting the presence of leukocytes and nitrites in the urine. While urine dipsticks give good results in young patients, they may not be able to accurately identify UTIs in older patients [4]. This inadequacy is probably due to the high prevalence of asymptomatic bacteriuria combined with the fact that the leukocyturia thresholds used to guide the diagnosis of UTIs are based on younger populations and may not be appropriate for older people [5]. Automated urine flow cytometers provide rapid and accurate counts of white blood cells, red blood cells, bacteria and epithelial cells in urine samples [6, 7]. As urine culture is time-consuming and does not aid the diagnosis of UTI in the emergency setting, several studies have established specific thresholds or scoring systems using these automated results to detect UTI or positive urine cultures [8, 9]. However, these studies have primarily focused on younger adults, limiting their relevance to older patients [10, 11].

Given these challenges, there is an urgent need to develop diagnostic criteria applicable to the older adults. This study proposes to investigate older patients admitted to the hospital with a urine culture obtained in the emergency department. The primary objective was to evaluate the flow cytometry parameters for the diagnosis of UTI in older patients and compare them with the performance of the urine dipstick. We also aimed to evaluate the association of biological parameters and clinical symptoms to exclude or diagnose UTI before urine culture results.

Materials and methods

Study population and data collection

This study included adult patients aged 65 years or older hospitalized at the Besancon University Hospital between May 2024 and October 2024 with a urine culture within the first 48 h of hospitalization. Urine samples obtained midstream or collected via in-out catheterization were accepted. Patients were excluded if (1) they had an indwelling catheter for more than 24 h, (2) they were undergoing antibiotic treatment prior to the urine culture being performed and (3) they had been hospitalized in the 3 previous months. Patients were prospectively included on a daily basis. Clinical and biological data were collected from the patients' medical records by two investigators (A.B and E.C.).

Urine analysis

Prior to the urine culture, the urine dipstick could be performed in an emergency setting using dipstick with automatic reading system (CLINITEK Status +, Siemens). Urine culture and urine cytology were performed as part of routine patient management. Urine cytology was performed using the Sysmex UF-4000 automated system (Sysmex, Kobe, Japan) according to the manufacturer's recommendations, which allowed counting of urinary white blood cells, bacteria, squamous cells, non-secretory cells (transitional cells and renal tubular cells), and atypical cells. Ten µl of urine was cultured on urine chromogenic agar plate (URI4 urine, Bio-Rad, Marnes-la-Coquette, France) and incubated at 35 °C for 24 to 48 h according to French recommendations. Bacterial identification was performed using MALDI-TOF MS technology (Bruker Daltonik GmbH, Bremen, Germany). Colony-forming units (CFU) were counted using a standard abacus and interpreted according to the French standard of medical microbiology (Table S1). Urine cultures were classified as (1) positive, defined as the presence of one or two uropathogens with a number of CFUs greater than the defined cut-off (Table S1), (2) negative, defined as the absence of a visible culture or with a number of CFUs less than the cut-off after 48 h, (3) contaminated, defined as the culture of 3 or more bacteria. Polymicrobial urine culture was defined as the presence of two uropathogens with a number of CFUs greater than the defined cut-off.

Diagnostic of UTI

The diagnosis of UTI in the older patients is complicated by the frequent absence of specific clinical signs in these patients. There is currently no gold standard for diagnosis in this age group [11]. We based the diagnosis of UTI on the clinician's assessment during the patient's admission, coupled with strict criteria. Patients were considered eligible for the UTI group if they were treated for UTI during their hospital stay based on their initial urine culture results. To confirm the diagnosis of UTI, patients had to have: a positive urine culture (as defined above) associated with a bloodstream infection with the same bacteria, or at least one major symptom of UTI (dysuria, pollakiuria), or imaging compatible with UTI, or at least two minor symptoms among: fever or chills, hypotension, confusion, urological obstruction, or flank pain without another diagnosis to explain these symptoms. Additionally, we collected other symptoms, such as onset of incontinence, acute urinary retention, or acute renal insufficiency. However, these symptoms were not included in our criteria, as they are not usually considered in the diagnosis of UTI. U-WBC, as a diagnostic criterion, was excluded to avoid biasing the leukocyte threshold selection. For patients with discordant classification between the patient's hospital admission report and our definition, patient's charts were reviewed by a geriatrician and an infectious disease physician independently (M.G. and K.B.). In the case of a discordant classification between the two investigators or a lack of data to exclude or confirm urinary tract infection, the patient was excluded.

Statistical analysis

Baseline characteristics were compared using Pearson's Chi-squared test or Fisher's exact test for categorical variables and Student's t-test for continuous variables. Multivariable logistic regression was performed for categorical variables with p-value < 0.05 in univariate analysis. Receiver operating characteristic (ROC) curves for quantitative parameters were plotted using the pROC package in R. Parameters with an area under the curve (AUC) greater than 0.80 were considered relevant [10]. AUCs were compared using the DeLong test. When AUC were from different datasets, we considered two AUCs to be different if the confidence interval did not overlap. Multiple comparisons of urine culture results according to Sysmex parameters were performed using the Kruskal-Wallis test, followed by Dunn's post-hoc test, corrected by the Bonferroni method. Sensitivity and specificity were compared using a proportion comparison test (z-test). A p-value < 0.05 was considered statistically significant for all tests. Thresholds were considered based on sensitivity, specificity, positive likelihood ratio (LR+) to predict UTI and negative likelihood ratio (LR-) to exclude UTI. Thresholds obtained for biological parameters were considered useful in clinical use to exclude UTI if LR- ≤ 0.1 or to confirm UTI if LR + ≥ 10 [12, 13]. All analyses were performed using R studio v4.2.3.

Ethics statement

The study was approved by the Institutional Review Board of Besançon University Hospital. According to following decree in the French Public Health Code: Décret n° 2017 – 884 du 9 mai 2017, this study does not involve human person and thus cannot be submitted to any French Institutional Ethics Committee. However, all patients gave their consent for the use of their data for research purposes.

Results

Patient inclusion

For the 6-month period, 462 patients were prospectively included. Eighty-one patients were eligible for the UTI group based on the clinician's diagnosis and treatment decision during their hospital stay. Of these, 60 patients met our criteria for a diagnosis of UTI (Fig. 1). The review of the 21 medical records by the 2 physicians led to the classification of 9 patients as having a UTI, 6 patients as having urinary tract colonisation and 6 patients as being excluded because it was impossible to reach a conclusion. Consequently, a total of 69 patients with UTI were considered for further analysis, alongside 387 control group patients. Patient age, number of prescribed medications, Charlson comorbidity score, and hospital setting were not significantly different between the UTI and control groups. The male/female ratio was different, with more males in the control group ($n = 200$; 51.7%) than in the UTI group ($n = 23$; 33.3%) ($p < 0.01$). Demographic data are shown in Table 1. Diagnoses made in the emergency department are available in Table S2.

Culture results

Of the 69 UTI cases, 97.1% had positive cultures, while two cultures were considered contaminated. In contrast, the control group had 25.8% positive cultures, 42.9% negative cultures, and 31.3% contaminated cultures. *Enterobacterales* were predominant in both groups, found in 91.9% of UTI cases ($n = 68$) and 79.8% of control samples ($n = 87$). *Escherichia coli* was the most common species in the UTI group ($n = 49$; 66.2%), followed by *Klebsiella* spp. ($n = 9$; 12.2%) and *Proteus* spp. ($n = 6$; 8.1%). Similarly, *E. coli* ($n = 71$; 64.45%), *Klebsiella* spp. ($n = 9$; 8.26%), and *Enterococcus* spp. ($n = 9$; 8.26%) were the main species in the control group (Table S3).

Clinical symptoms

In the UTI group, 52.2% ($n = 36$) of patients had a major symptom compared to 7.2% ($n = 28$) in the control group ($p < 0.001$) (Table 1). Except for confusion ($p = 0.825$) and hypotension ($p = 0.164$), all other minor symptoms used for diagnosis were associated with the UTI group in univariate analysis ($p < 0.05$). Onset of incontinence, which was not in our diagnostic criteria, was also associated with the UTI group in univariate analysis ($p < 0.001$). The multivariable logistic regression model indicated significant associations with UTI for dysuria (OR 11.1 [4.87–25.9]), pollakiuria (OR 7.24 [2.94–18.0]), onset of incontinence (OR 6.02 [1.83–20.0], lower back pain (OR 3.53 [1.27–9.44]), and fever or chills (OR 2.80 [1.49–5.30]). However, urinary tract obstruction did not show a significant association with UTI (OR 3.32 [0.641–16.6]). Minor clinical criteria were present in 25 patients (36.2%) in the UTI group and 51 patients (13.2%) in the control group (specificity of 86.8% [83.09–89.83] and a LR + of 2.75 [2.31–3.28]). By defining minor clinical criteria as the presence of at least two significant symptoms, including onset of incontinence, lower back pain, and fever or chills, we could identify 18 patients (26.1%) in the UTI group, compared to 10 patients (2.6%) in the control group (specificity of 97.42% [95.31–98.59] and a LR + of 10.10 [6.10–16.72]).

Biological parameters and threshold determination

In univariate analysis, parameters including urinary bacterial count (UBC), urinary white blood cell count (U-WBC), C-reactive protein (CRP), white blood cell, transitional cells, squamous cells, and atypical cells were significantly higher in patients with UTI ($p < 0.05$) (Table 1). The ROC curves demonstrated excellent discriminatory ability for both UBC (AUC = 0.874

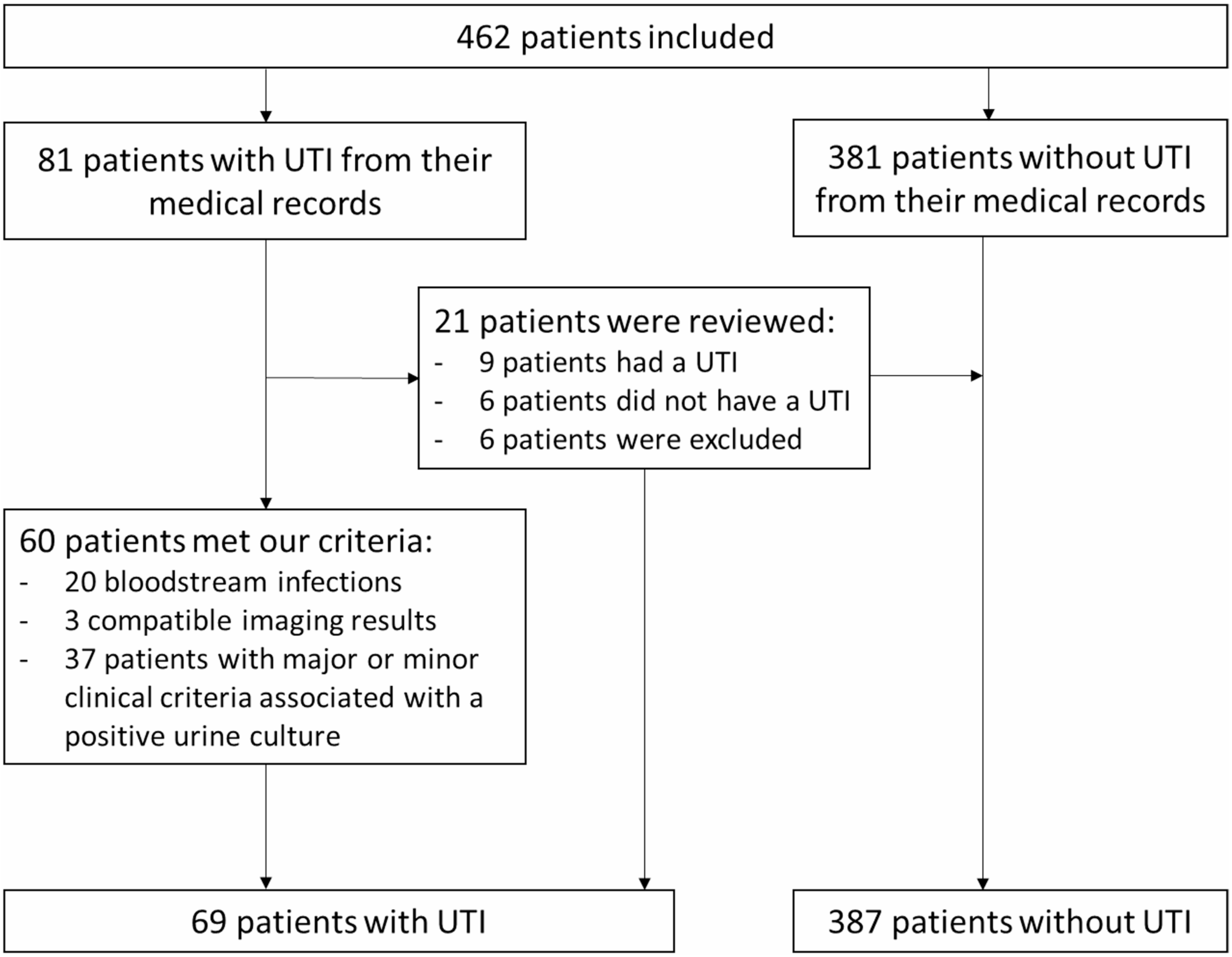

Fig. 1 Flow chart of patient enrolment

[0.841–0.906]) and U-WBC (AUC = 0.925 [0.896–0.954]) (Fig. 2A). In contrast, CRP (AUC = 0.673 [0.608–0.738]), blood white blood cells (AUC = 0.613 [0.540–0.686]), squamous cells (AUC = 0.641 [0.578–0.713]), transitional cells (AUC = 0.688 [0.621–0.755]), and atypical cells (AUC = 0.641 [0.578–0.703]) did not demonstrate sufficient predictive value for further analysis (AUC < 0.8).

Sensitivity, specificity and LR- were calculated for U-WBC and UBC thresholds (Table S4). Two thresholds with LR- < 0.1 were considered interesting for clinical use. A threshold of 50 leukocytes/µL had a sensitivity of 94.2% [85.8–98.4], a specificity of 74.4% [69.8–78.7], and a LR- of 0.08 [0.05–0.13]. A threshold of 110 leukocytes/µL had a sensitivity of 89.9% [80.2–95.8] and a specificity of 83.2% [79.1–86.8] and a LR- of 0.12 [0.09–0.16]. For UBC, a threshold of 150 bacteria/µL had a sensitivity of 98.6% [92.2–100], a specificity of 68.5% [63.6–73.1], and a LR- of 0.02 [0.003–0.15]. By combining UBC and U-WBC, we identified new threshold at < 300 bacteria/µL and < 300 leukocytes/µL achieving a sensitivity of 98.55% [92.24–99.74], a specificity of 72.35% [67.69–76.57], and a LR– of 0.02 [0.003–0.14] (Fig. S1).

Culture thresholds

We aimed to evaluate Sysmex parameters to predict urine culture positivity (Fig. S2). Both a high UBC and a high U-WBC were associated with a positive urine culture ($p < 0.001$). We did not observe statistical difference between positive urine culture and culture with more than three bacteria (considered as contamination) for epithelial cells ($p > 0.99$), squamous cells ($p > 0.99$), non-secretory cells ($p > 0.99$) and transitional cells ($p > 0.99$). The ROC curve AUC was above 0.8 for UBC (AUC = 0.923 [0.895–0.950]) and for U-WBC (AUC = 0.853 [0.819–0.888]) (Fig. 2B). The AUC for UBC was significantly higher than the AUC for U-WBC ($p < 0.001$). The optimal threshold defined by the Youden index was 1176 bacteria/µL, giving a sensitivity of 79.17% [72.41–84.62], specificity of 95.83% [92.86–97.6], LR- of

Table 1 Baseline characteristics, symptoms, and biological parameters of 456 patients with and without a urinary tract infection. Biological parameters are expressed as mean (SD). A p-value < 0.05 was considered significant

		UTI group n = 69 (%)	Control group n = 387 (%)	*p*-value	OR
Baseline characteristics					
Sex (male)		23 (33.3%)	200 (51.7%)	**< 0.01**	**-**
Age (years), mean, (SD)		81.92 (8.3)	81.61 (8.6)	0.438	-
CCI, mean, (SD)		1.84 (1.7)	1.90 (2.0)	0.809	-
Medical departments		61 (88.4%)	344 (88.9%)	> 0.999	-
Number of medications, mean, (SD)		6.97 (3.9)	7.10 (4.3)	0.797	-
Living in an institution		10 (14.5%)	26 (6.7%)	**0.050**	-
Symptoms and signs					
Major symptoms:		36 (52.2%)	28 (7.2%)	**< 0.001**	**-**
	Dysuria	23 (33.3%)	15 (3.9%)	**< 0.001**	**< 0.001**
	Pollakiuria	21 (30.4%)	14 (3.6%)	**< 0.001**	**< 0.001**
Minor symptoms:		25 (36.2%)	51 (13.2%)	**< 0.001**	**-**
	Fever / chills	43 (62.3%)	103 (26.6%)	**< 0.001**	**< 0.01**
	Confusion	12 (17.4%)	75 (19.4%)	0.825	-
	Hypotension	13 (18.8%)	46 (11.9%)	0.164	-
	Flank pain	14 (20.3%)	18 (4.6%)	**< 0.001**	**< 0.01**
	Urological obstruction	6 (8.7%)	5 (1.3%)	**< 0.01**	0.143
Onset of incontinence		10 (14.5%)	7 (1.8%)	**< 0.001**	**< 0.01**
Acute renal insufficiency[1]		19 (27.5%)	82 (21.2%)	0.311	
Acute urinary retention		13 (18.8%)	43 (11.1%)	0.109	
Biological parameters					
C-reactive protein (mg/L)		115.54 (103.3)	69.77 (91.7)	**< 0.001**	**-**
Blood leukocyte (G/L)		12.57 (5.1)	10.70 (5.1)	**< 0.01**	**-**
Urinary red blood cell/µL		174.97 (779.6)	709.88 (7218.4)	0.154	-
Urinary leukocyte/µL		4,098 (9,138)	133.26 (496.2)	**< 0.001**	**-**
Transitional cell/µL		1.29 (3.3)	0.42 (0.84)	**0.034**	**-**
Atypical cell/µL		0.30 (0.90)	0.04 (0.22)	**0.017**	**-**
Non-secretory cell/µL		6.34 (8.1)	5.41 (10.7)	0.403	-
Squamous cell/µL		13.88 (18.3)	8.13 (19.0)	**0.019**	**-**
Renal tubular cell/µL		5.02 (6.8)	4.97 (10.4)	0.951	-
Bacterial/µL		29,863 (30,964)	6,818 (18,147)	**< 0.001**	**-**

CCI: Charlson Comorbidity Index; OR: odds ratio; SD: standard deviation; UTI: urinary tract infection. [1]Data obtained from medical records

0.22 [0.21–0.23] and LR + of 19.0 [16.07–22.46]. No UBC threshold was able to achieve an LR- < 0.1.

Performance of urine dipstick

We collected the results of a total of 417 urine dipsticks (91.4%) performed in the emergency department, including 66 for the UTI group (95.6%) and 351 for the control group (90.7%). Urine dipsticks were considered negative if leukocyte esterase and nitrite were negative (AUC = 0.7405 [0.706–0.775]) and positive otherwise (Table S5). Sensitivity of urine dipstick for UTI (95.45% [87.47–98.44]) was lower than the sensitivity of UBC threshold of 150 bacteria/µL (98.48% [91.90–99.79]) ($p < 0.01$) but similar to the sensitivity of the U-WBC threshold of 50 leukocytes (95.45% [87.47–98.44]) ($p < 0.99$). However, specificity was higher for both the UBC threshold of 150 bacteria/µL (67.81% [62.75–72.48]) and the U-WBC threshold of 50 leukocytes (70.66% [65.69–75.17]) compared to the specificity of the urine dipstick (57.83% [52.61–62.89]) ($p < 0.001$ and $p < 0.01$, respectively). The LR- was < 0.1 for all test methods. Urine dipstick in patients with at least one major symptom had a sensitivity of 91.43% [77.62–97.04], a specificity of 73.08% [53.92–86.30], a LR- of 0.117 [0.059–0.234] and a LR + of 3.396 [2.55–4.42].

Analysis according to the sex of the patients

We performed a subgroup analysis to compare the performance of flow cytometry and urine dipstick according to the sex. We included 417 patients, 215 women (51.56%) and 202 men (48.44%). The AUC of the ROC curve for UBC was higher in men (0.966 [0.943–0.990]) than in women (0.7839 [0.722–0.846]) but no difference was observed for U-WBC between men (0.961 [0.926–0.995]) and women (0.880 [0.828–0.933]) (Fig. S3). Urine dipstick was considered acceptable for men

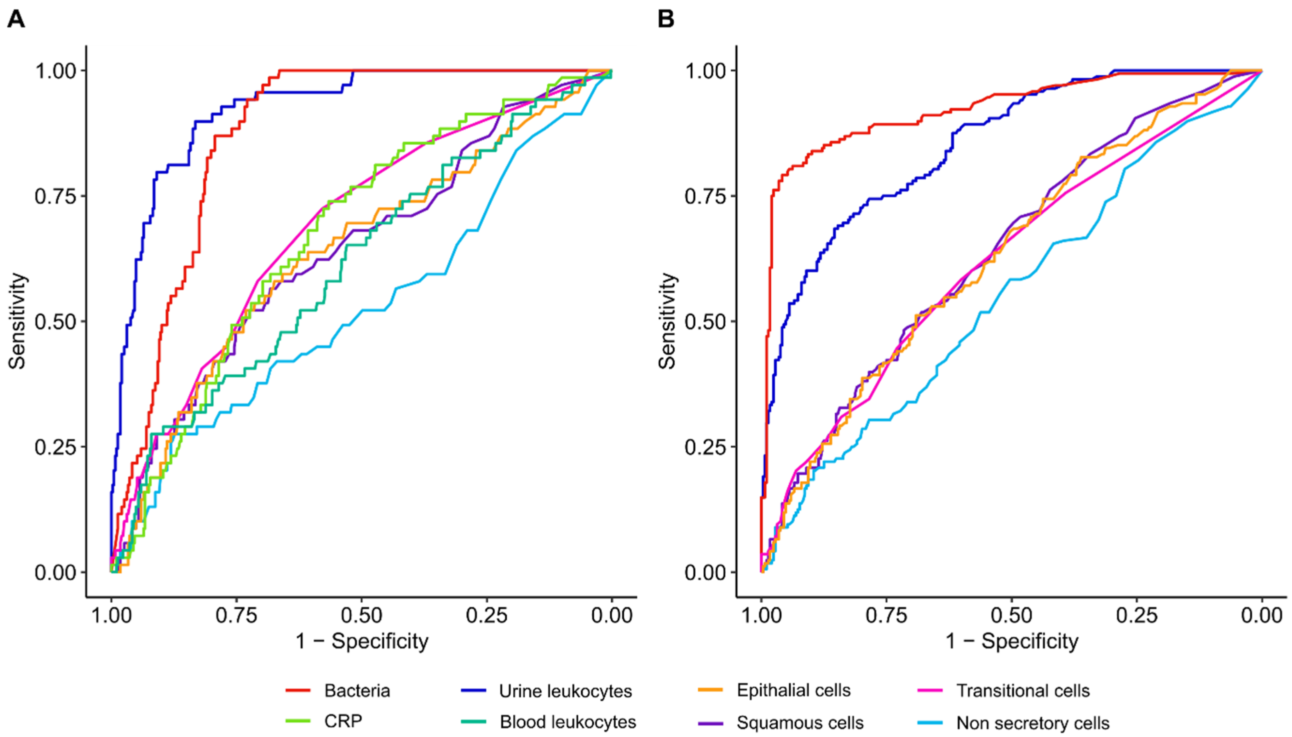

Fig. 2 Receiver operating characteristic curves of biological parameters (from urine using Sysmex UF-4000 or from blood analysis) predicting (**A**) urinary tract infection and (**B**) positive urine culture from 456 patients

(LR- < 0.1) but not for women (LR- = 0.129) (Table S6). However, a positive urine dipstick associated with the presence of a major symptom identified correctly 12 of 15 patients as having a UTI in men and 20 of 24 patients as having a UTI in women. UBC < 150 bacteria/µL was acceptable for both men and women (LR < 0.1), with an even better threshold for women of 300 bacteria/µL (sensitivity of 95.45% [84.86–98.74], specificity of 52.05% [44.6–59.41] and a LR- of 0.087 [0.03–0.24]). The optimal U-WBC threshold varied according to the sex of the patient. For men, a U-WBC < 250 leukocytes/µL had a sensitivity of 90.9% [72.18–97.47], a specificity of 95.6% [91.48–97.73], a LR + of 20.4 [15.85–26.39] and a LR- of 0.09 [0.036–0.25]. In women, a threshold of 40 leukocytes/µL provided the best compromise for ruling out a UTI, with a sensitivity of 95.4% [84.86–98.74], a specificity of 59.6% [52.16–66.71], a LR + of 2.37 [2.29–2.44] and a LR- of 0.076 [0.028–0.21]. Overall, all tested methods lacked specificity in women (35.1% for urine dipstick, 45.51% for UBC < 150 bacteria/µL, 52.0% for combined threshold < 300 for UBC and U-WBC). In men, all tested methods achieve an LR- < 0.1 and the combined threshold < 300 for UBC and U-WBC achieves an LR + at 10.00 [8.97–11.15]. Based on our results, we developed two algorithms for the diagnosis of UTI in older women and men.

In men, the proposed algorithm (Fig. 3) in the absence of flow cytometry successfully excluded 173 of 180 (96.1%) patients without UTI and correctly diagnosed 14 of 22 (63.6%) patients with UTI. Using flow cytometry bacterial count parameters, the algorithm excluded 167 of 180 (92.8%) patients without a UTI and correctly diagnosed 15 of 22 (68.2%) patients with a UTI. Similarly, in women (Fig. 4), a U-WBC threshold of 40 leucocytes/µL, combined with the major symptom criteria, excluded 114 of 187 patients (61.0%) and correctly diagnosed 22 of 44 (50%) patients with UTI. Using flow cytometry bacterial count parameters, the algorithm excluded 125 of 187 (66.8%) patients without a UTI and correctly diagnosed 22 of 44 (50%) patients with UTI. Minor symptom criteria did not add value to the algorithm in older women.

Discussion

The diagnosis of UTI in older patients is challenging. In this study, we conducted a comprehensive analysis of Sysmex urine parameters in conjunction with detailed clinical symptoms. Our findings revealed that current leukocyturia thresholds are not appropriate in both men and women. There are differences between the genders, suggesting the need to set appropriate threshold according to the sex of the patient, as we do for CFU thresholds in urine culture. We also identified bacteriuria as a parameter of interest with both a threshold to exclude urine culture positivity and a threshold to predict the urine culture positivity. Finally, urine dipstick is useful to

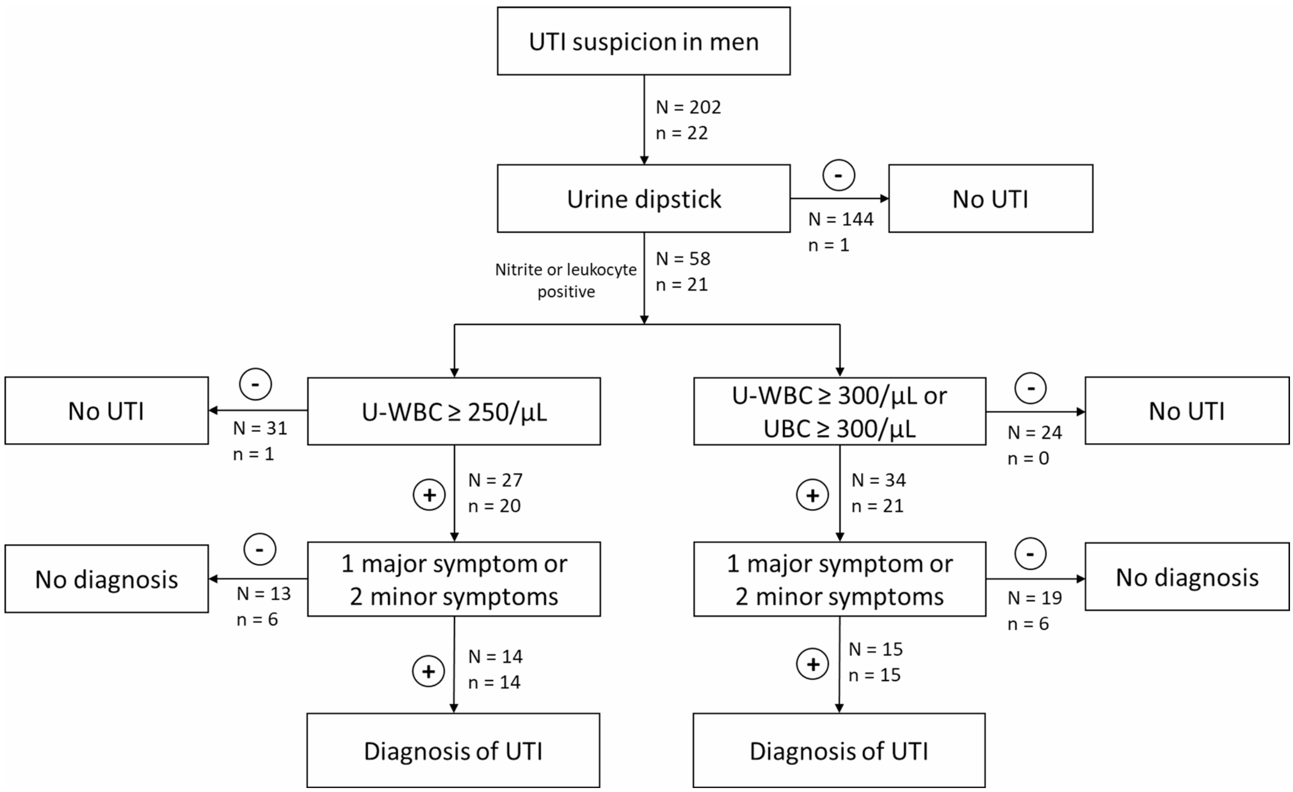

Fig. 3 Proposed algorithm for the diagnosis of urinary tract infection in older men without urinary tract material. N: total number of patients; n: number of patients with urinary tract infection among N; UTI: urinary tract infection; U-WBC: urine white blood cell count; UBC: urine bacterial count

exclude UTI in older men but its benefit is more questionable in older women.

One of the primary limitations in studies on UTIs in the older adults is the absence of a gold standard in UTI diagnosis [11]. Physicians tend to overestimate the number of UTIs, leading to the overprescription of antibiotics in this population [14]. To categorize patients more accurately, we implemented several diagnostic steps. Patients needed to be hospitalized for at least 48 h, allowing us to assess emergency diagnosis and microbiological results. We chose clinically frequent criteria and categorized them into major symptoms (pollakiuria, dysuria) and minor symptoms (flank pain, fever, urinary obstruction, hypotension, and confusion) [4, 5, 11, 15]. We observed a notable association between the onset of incontinence and the diagnosis of UTI. A meta-analysis found that while incontinence was a specific indicator for UTI in men, it lacked sensitivity in both men and women, with variations in data collection methods across studies [2]. Another study reported that although incontinence was not part of the diagnostic criteria, it was present in 49% of older female UTI patients [5]. Conversely, some studies did not include incontinence from their diagnostic criteria for UTI [4, 15]. Initially, we did not include incontinence as part of our diagnostic criteria. However, following statistical analysis, we found that the onset of incontinence was highly specific to UTI, as only 1.8% of patients in the control group exhibited this symptom. Our findings suggest that the onset of incontinence could be used as a diagnostic criterion for UTI in older for further studies.

We identified an optimal leukocyturia threshold of 50 leukocytes/µL in our population, higher than the recommended threshold of 10 leukocytes/µL [16, 17]. To increase specificity, a higher threshold of 110 leukocytes/µL could be useful for confirming, rather than excluding, a UTI.Two studies of Bilsen et al., also suggest higher threshold. The first in a multidisciplinary consensus study, suggested that leukocyturia should be categorised for all aged patients as less than 10/µL, between 10/µL and 200/µL, and greater than 200/µL for the general population [11]. In the second study, Bilsen et al., suggested in women over 65 years of age that a threshold of 10 leukocytes/µL is not appropriate and have proposed several thresholds above 100 leukocytes/µL with a Youden's index of 264 leukocytes/µL [5]. The difference observed with our threshold of 40 leukocytes/µL in older women to exclude UTI may be explained by the relatively small size in both studies. Moreover, patients included in the study of Bilsen et al. had more symptoms (77.8% of patients with dysuria and 90.5% of patients with frequency), which may give a higher specificity in the

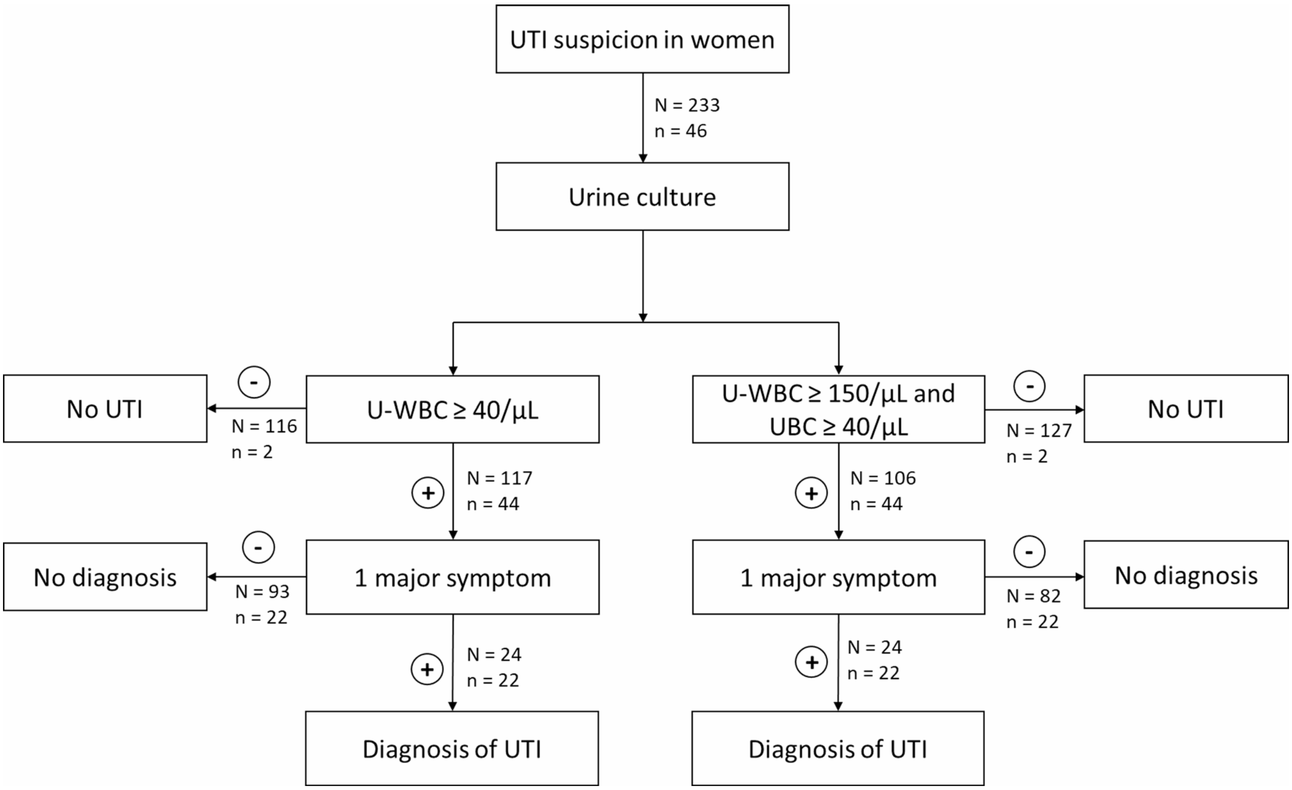

Fig. 4 Proposed algorithm for the diagnosis of urinary tract infection in older women without urinary tract material. N: total number of patients; n: number of patients with urinary tract infection among N; UTI: urinary tract infection; U-WBC: urine white blood cell count

calculation of the LR-. To our knowledge, our study is the first to propose a urine leukocyte threshold in older men using flow cytometry analysis. We find that U-WBC is an excellent marker of UTI with an AUC of 0.960, giving a U-WBC threshold of 250 leukocytes/µL, which gives both an LR + > 10 and an LR- 0.1. However, we included only a small number of male patients with UTI. Larger multicentre studies are needed to reassess the optimal leukocyturia threshold for older patients.

There is actually no recommended threshold for UBC interpretation using Sysmex automate. However, in our study we found that UBC are more suitable than urine dipstick in excluding the diagnosis of UTI in both men and women with a threshold of 150 bacteria/µL. In women, this threshold can be up to 300 bacteria/µL to gain specificity. The combination of UBC and U-WBC gave a gain in sensitivity and specificity for the diagnosis of UTI. Thus, at a threshold of 1176 bacteria/µL, we were able to predict urine culture positivity with an LR + of 19. This threshold is concordant with a previous study which obtained an AUC between 0.897 and 0.952 (0.923 in our study) according the number of CFU/mL in urine culture [18]. Analysis of epithelial cell counts measured by the Sysmex UF-4000 was not effective in discriminating between patients with and without UTI or in predicting urine culture positivity or contamination. This finding contrasts with the proposed threshold of 30 squamous cells/µL used to classify urine cultures as contaminated [19].

Urine dipsticks are used as a first-line test to exclude UTI in women or to confirm UTI in men [17, 20, 21]. The use of urine dipsticks for diagnosing cystitis is rated as a weak strength, and their use leads to only a modest increase in diagnostic accuracy when applied to patients with typical symptoms, according to the European Association of Urology (EAU) [22]. The European federation of clinical chemistry and laboratory no longer recommends urine dipsticks for diagnosing UTIs in young women [23]. The infectious diseases society of America (IDSA) guidelines were published in 2011 and an updated version is currently in development. Our results suggest that urine dipstick is a good test to exclude UTI in older men (LR- of 0.057) but not in women (LR- of 0.129). Urine dipstick alone was not able to confirm UTI in either men (LR + of 4.64) or women (LR + of 1.15). Similar to Advani et al., urine dipstick performed better in older men than in older women [4]. Our results suggest that urine dipstick is a good test to exclude UTI in older men, but less good in older women to exclude or diagnose UTI.

Similar studies used the IQ200 automated urine analyzer, but the UBC results cannot be extrapolated to those obtained with the Sysmex. Most studies of Sysmex or IQ200 analysis have used a positive urine culture as the gold standard for calculating urine leukocyte and bacterial thresholds [10, 24–26]. However, this approach does not include clinical data, so misclassification is likely and may not represent patients with UTI. Foudraine et al.. used clinical data to create a clinical-biological score to predict UTI in the general population using the IQ200 [8]. They also showed that the urine leukocyte cut-off of 10/µL was too low for general population and used a similar threshold of 50 leukocytes/µL (sensitivity 91% vs. 94% in our study; specificity 79 vs. 74% in our study).

Based on our results in older men, the urine dipstick test remains an effective method for excluding UTI, whereas in older women we recommend direct urine culture. Each algorithm offers two options: one based on a U-WBC threshold and another designed exclusively for Sysmex users, which requires UBC. Both UBC and U-WBC can exclude UTI without the need for clinical symptoms prior to urine culture results. Clinical symptoms in men, and major symptoms in women, when associated with UBC or U-WBC, were specific to UTI.

Current recommendations for diagnosing urinary tract infections in older patients are not appropriate. Urine flow cytometry adds value by defining new thresholds for UBC or U-WBC that can exclude UTI before urine culture results. Biological parameters varied between men and women, suggesting that different recommendations are needed depending on the gender of the patient. In addition, specificity for UTI diagnosis in older women remains poor with any method. The urine dipstick is still valuable to exclude UTI in older men, but not in older women. However, we performed a monocentric study with relatively few patients with UTI, which needs to be confirmed by large multicentre studies.

Supplementary Information

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Supplementary Material 1

Author contributions

AB designed the work, collected and interpreted the data, and drafted the manuscript. EC collected the data and revised the manuscript substantially. MC interpreted the data and revised the manuscript substantially. HGH designed the work and revised the manuscript substantially. IP interpreted the data and revised the manuscript substantially. KB interpreted the data and revised the manuscript substantially. XB designed the work and made a substantial contribution to drafting the manuscript. All authors read and approved the final version of the manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Human ethics and consent to participate

The study was approved by the Institutional Review Board of Besançon University Hospital and conducted in accordance with the principles of the Declaration of Helsinki. As this was an observational study, it did not require submission to a French Institutional Ethics Committee. In accordance with the French regulatory framework (GDPR, French Data Protection Act, Public Health Code, and RGOS), patients were informed about the use of their data during hospitalization and had the right to refuse participation in any study. In France, observational studies can be conducted based on the patient's right to object, meaning that patients must be informed about the use of their data and have the possibility to oppose it.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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