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Research Article

Urine Testing for the Detection of Urinary Tract Infections in Febrile Pediatric Cancer Patients Presenting to the ED

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ABSTRACT

Introduction: Urinary Tract Infections (UTIs) are prevalent in pediatric cancer patients, but usually present vaguely, with non-localizing signs and symptoms (i.e., with fever but without urinary symptoms), especially in the setting of febrile neutropenia, rendering the diagnosis challenging. There is still much controversy when it comes to the indications of urine testing in pediatric cancer patients presenting with fever, but without urinary signs or symptoms.

Objectives: Our aim was to determine the value of obtaining a Urine Culture (UC) in pediatric cancer patients presenting with fever only, as well as to evaluate the diagnostic performance of a Urine Analysis (UA) in this group.

Methods: This was a retrospective cohort study conducted on asymptomatic pediatric cancer patients presenting to our Emergency Department (ED) solely with fever, over a period of five years.

Results: A total of 301 patients were included in this study. The mean age was 7.98 ± 4.98 years. A patient with a positive UC was more likely to be a female ($p<0.001$) and to have a liquid tumor ($p=0.024$). More than half of the patients with a positive UC had a negative UA ($p<0.001$). A UA was found to be 44.8% sensitive and 90.4% specific for the diagnosis of a UTI in the studied population, with a positive predictive value of 33.3% and a negative predictive value of 93.9%.

Conclusion: A positive UC remains the gold standard and classical method for the diagnosis of a UTI in all patients in general, and in febrile pediatric cancer patients in specific. Although cheaper and more timesaving, a UA has a very limited role in making an absolute diagnosis when compared to a UC.

Keywords: Cancer; Febrile neutropenia; Pediatrics; Urine testing; Urinary tract infections

INTRODUCTION

Febrile illness is a commonly feared complication of cancer and cancer treatment [1]. Whether accompanied by neutropenia or not, fever was shown to be associated with high mortality rates in pediatric cancer patients. This is mainly due to the remarkably increased risk of serious infections, specifically bacterial, in this patient group [1,2]. The early diagnosis of infections among these patients is challenging as they mostly present with few non-localizing clinical signs and symptoms such as fever, headache, and hypotension [3]. Nevertheless, without prompt accurate diagnosis and the initiation of broad-spectrum antibiotics, infections can rapidly progress to sepsis and result in death [4].

Among the most prevalent bacterial infections in pediatric cancer patients with cancer are Urinary Tract Infections (UTIs) [5]. In this context, Olad et al. [6] and Jimeno et al. [7] have found that the most common sites of infection in Febrile Neutropenic (FN) patients were the oral mucosa, followed by the respiratory tract, urinary tract, and gastrointestinal tract. Hence, it is critical to meticulously diagnose and appropriately treat a UTI in this population, to prevent further ascension, determine any future risk

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of similar infections, and avoid long-term residual renal disease [8].

Diagnosing UTIs in pediatric cancer patients is primarily based on the results of a Urine Analysis (UA) and Urine Culture (UC). While a UC is perceived to be the gold standard diagnostic tool, its result is not readily available at the time of initial evaluation and requires a minimum of 24 hours [9,10]. Given the grave sequelae of untreated infections in pediatric cancer patients, particularly in the setting of neutropenia, such a delay is not favorable and better be avoided. A quicker, simpler, and cheaper alternative would be screening for pyuria on a UA, especially where facilities for UC are unavailable [9,11]. Still, some physicians emphasize the requirement of obtaining a UC, as they have shown that a positive UC in children with cancer, specifically those who are neutropenic, may not be associated with UA abnormalities [12].

When it comes to the established guidelines, there is less agreement regarding the value of a UC as a routine investigatory tool [13]. According to the practice guidelines of the Infectious Diseases Society of America (IDSA) on adult and pediatric FN cancer patients, a UC is only indicated if patients present with urinary signs or symptoms, have a foley catheter, or have a positive UA [14,15]. However, unlike acute respiratory or gastrointestinal tract infections, UTIs are usually subtle in pediatric cancer patients, presenting without localizing signs or symptoms, rendering the clinical picture very non-specific. In fact, fever might be the only symptom upon initial presentation in these patients [16]. Consequently, a high percentage of UTIs in the studied population goes missed, except when a UC is routinely obtained as part of the diagnostic workup of FN patients [12]. While IDSA guidelines need certain criteria to be met before ordering a UC, we find specialists from all over the world recommending the integration of urine testing in the basic evaluation panel of any FN patient before administering antibiotics [17]. Here, it is worth noting that, unlike FN patients, those who are febrile but non-neutropenic are much less addressed in the literature, and recognized standards on their management are lacking [18].

Considering this controversy and given the paucity of data especially on non-neutropenic febrile patients, we aimed to assess the utility of urine studies in detecting UTIs in pediatric cancer patients presenting to the Emergency Department (ED) with fever, but without urinary signs or symptoms.

METHODOLOGY

Study design and setting

This was a retrospective cohort study conducted on all pediatric cancer patients who presented to the ED of the American University of Beirut Medical Center (AUBMC), between January 1, 2013, and December 31, 2018, with fever but without any urinary signs or symptoms.

To note, AUBMC is a major cancer referral center in Lebanon, receiving as many as 56,000 ED visits every year. Our ED is the only in Lebanon that offers specialized pediatric emergency medicine services. AUBMC is home to the Children's Cancer Center of Lebanon (CCCL), the main pediatric oncology provider in Lebanon that, at any time, cares for around 350 patients with cancer in AUBMC and other partner hospitals. Acute visits for our target population takes place in the CCCL outpatient department during their working hours, and in the ED during off hours.

Ethical approval was obtained from the Institutional Review Board (IRB) at AUBMC under the protocol number (BIO-2019-0198).

Study population

This study included all pediatric patients with an active oncological disease (<18 years old) who presented to the ED or CCCL outpatient clinics of AUBMC with fever. Only patients who had no urinary signs or symptoms and had their urine tested as part of the standard diagnostic workup during the index visit were eligible for inclusion.

- We defined fever as a single oral temperature ≥ 38.3°C in FN patients, or a temperature ≥ 38°C persisting for more than one hour, or two reasings >38°C during a 12-hour period [1].
- We defined urinary signs and symptoms as any of the following documented in the patient's chart during the index visit: frequency, dysuria, hematuria, changes to continence, suprapubic/inguinal pain or tenderness or costo vertebral pain or tenderness.
- We defined a positive UC using the cutoff of ≥ 100,000 Colony Forming Units (CFU)/ml. Patients with Vesico Ureteral Reflux (VUR), genitourinary malignancies, who have received bone marrow or stem cell transplant, or those who were receiving antibiotics (other than prophylactic antibiotics) within two weeks from presentation were excluded from the analysis.

Data collection and sampling

We reviewed the charts of all patients 1 month to 18 years of age who were seen at least once by the CCCL department and presented to the ED during our pre-specified time frame. Charts were originally handwritten but later scanned into the electronic health record of the patient where laboratory and imaging results were also documented. We reviewed all visits and listed all those which were due to a febrile illness. We then did a random sampling to identify one febrile visit for each patient, which was considered the index visit.

Following an IRB-approved unified data collection manual that was adjusted after pilot data collection, the team used the same nomenclature, definitions, and workflow to retrieve the data. We did a quality check after 50% of the records were collected and improved our data collection accordingly. We collected data on patient demographics, oncological history, treatment history (in terms of chemotherapy/surgical intervention), information related to the identified ED visit (such as laboratory investigations, infectious workup, and radiologic studies conducted in the ED), as well as patient outcomes. Data on the illness presentation were retrieved from the scanned hand-written charts, while laboratory data and metrics were retrieved from electronic records.

Statistical analysis

Statistical analyses were performed using Stata MP version 13.0 (College Station, TX: StataCorp LP). Descriptive analysis was conducted with continuous variables presented as mean ± Standard Deviation (SD) and categorical variables expressed as frequencies and percentages. Bivariate analysis was also done to compare patients with a positive and negative UC.

Student's t-test and Wilcoxon Rank-sum test were used for continuous variables, whereas Chi-squared and Fisher's exact tests were used for categorical variables. All tests were interpreted at alpha of 0.05.

Accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were calculated for UA and for each component of the UA. The analysis was performed to determine the value of urine studies in diagnosing UTIs in asymptomatic febrile pediatric cancer patients, with a UC being considered the golden diagnostic tool. We used the value ≥ 100,000 CFU/ml as the cutoff to define a positive UC.

RESULTS

Characteristics of patients

A total of 301 patients were included in this study, with a mean age of 7.98 ± 4.98 years. The greater percentage of the included patients were males (56.1%), had liquid tumors (52.2%), and were neutropenic (58.1%). A positive UC was documented in 29 patients (9.6%). Most patients with a positive UC were females (82.8%, p<0.001) and had liquid tumors (72.4%, p=0.024) (Table 1).

Table 1: Baseline characteristics of patients with positive vs. negative urine culture (UC).

Variables	All patients N=301 (100.0%)	Positive UC n=29 (9.6%)	Negative UC n=272 (90.4%)	P-value
Age, mean ± SD	7.98 ± 4.98	7.6 ± 5.1	8.03 ± 4.98	0.636
Females, n (%)	132 (43.9%)	24 (82.8%)	108 (39.7%)	<0.001
Males, n (%)	169 (56.1%)	5 (17.2%)	164 (60.3%)	
Tumor type, n (%)				
Solid	143 (47.5%)	8 (27.6%)	135 (49.6%)	0.024
	158 (52.5%)	21 (72.4%)	137 (50.4%)	
Liquid				
ANC1, mean ± SD	2568.6 ± 4162.1	4561.7 ± 7080.1	2356.1 ± 3677.98	0.109
Neutropenia, n (%)				
Yes	175 (58.1%)	12 (41.4%)	163 (59.9%)	0.054
No	126 (41.9%)	17 (58.6%)	109 (40.1%)	
Neutropenia[2], n (%)				
Mild	21 (12.0%)	1 (8.3%)	20 (12.3%)	0.475
Moderate	19 (10.9%)	1 (8.3%)	18 (11.0%)	
Severe	51 (29.1%)	6 (50.0%)	45 (27.6%)	
Profound	84 (48.0%)	4 (33.3%)	80 (49.1%)	

Note: [1]ANC: Absolute Neutrophilic Count, reported as mean ± standard deviation (SD)

[2]Neutropenia is divided into mild (1000<ANC<1500 cells/mm^3), moderate (500<ANC<1000 cells/mm^3), severe (100<ANC<500 cells/mm^3) and profound (<100 cells/mm^3).

Neutropenic patients constituted more than half (58.1%) of our population. Neutropenic patients were significantly older than their non-neutropenic counterparts (8.6 ± 4.9 vs. 7.1 ± 4.9, p=0.008). Moreover, neutropenia was more significantly encountered in patients with liquid tumors than in those with solid tumors (59.4% vs. 40.6%, p=0.005) (Table 2a).

Table 2a: Baseline characteristics of patients with Febrile Neutropenia (FN) vs. Febrile Non- Neutropenia (non-FN).

Variables	All patients N=301 (100.0%)	FN n= 175 (58.1%)	Non-FN n= 126 (41.8%)	P-value
Age, mean ± SD	7.98 ± 4.98	8.6 ± 4.9	7.1 ± 4.9	0.008
Females, n (%)	132 (43.9%)	75 (42.9%)	57 (45.2%)	0.681
Males, n (%)	169 (56.1%)	100 (57.1%)	69 (54.8%)	
Tumor type, n (%)				
Solid	143 (47.5%)	71 (40.6%)	72 (57.1%)	0.005
Liquid	158 (52.5%)	104 (59.4%)	54 (42.9%)	
ANC1, mean ± SD	2568.6 ± 4162.1	295.6 ± 402.2	5725.5 ± 4906.3	<0.001
Urine culture, n (%)				
Positive	29 (9.6%)	12 (6.9%)	17 (13.5%)	0.054
Negative	272 (90.4%)	163 (93.1%)	109 (86.5%)	

Note: 1ANC: Absolute Neutrophilic Count, reported as mean ± standard deviation (SD).

A UC was positive in 6.9% of FN patients. A positive UC in neutropenic patients was significantly associated with female sex (75%, p=0.02) (Table 2b).

Table 2b: Baseline characteristics of FN patients with positive UC vs. negative UC.

Variables	All FN patients N=175 (100.0%)	Positive UC n=12 (6.9%)	Negative UC n=163 (93.1%)	P-value
Age, mean ± SD	8.6 ± 4.9	7.38 ± 4.27	8.73 ± 4.95	0.36
Female, n (%)	75 (42.9%)	9 (75.0%)	66 (40.5%)	0.02
Tumor type, n (%)				
Solid	71 (40.6%)	2 (16.7%)	69 (42.3%)	0.126
Liquid	104 (59.4%)	10 (83.3%)	94 (57.7%)	
ANC1, mean ± SD	295.6 ± 402.2	314.7 ± 393.5	294.2 ± 403.97	0.866
Neutropenia[2], n (%)				
Mild	21 (12.0%)	1 (8.3%)	20 (12.3%)	0.475
Moderate	19 (10.9%)	1 (8.3%)	18 (11.0%)	
Severe	51 (29.1%)	6 (50.0%)	45 (27.6%)	
Profound	84 (48.0%)	4 (33.3%)	80 (49.1%)	

Note: 1ANC: Absolute Neutrophilic Count, reported as mean ± standard deviation (SD).

[2]Neutropenia is divided into mild (1000<ANC<1500 cells/mm^3), moderate (500<ANC<1000 cells/mm^3), severe (100<ANC<500 cells/mm^3) and profound (<100 cells/mm^3).

A UC was positive in 13.5% of non-FN patients. A positive UC in non-neutropenic patients was also significantly associated with female sex (88.2%, p<0.001) (Table 2c).

Table 2c: Baseline characteristics of non-FN patients with positive vs. negative UC.

Variables	All non-FN patients N=126 (100%)	Positive UC n=17 (13.5%)	Negative UC n=109 (86.5%)	P-value
Age, mean ± SD	7.08 ± 4.97	7.7 ± 5.79	6.99 ± 4.85	0.585
Female, n (%)	57 (45.2%)	15 (88.2%)	42 (38.5%)	<0.001
Tumor type, n (%)				
Solid	72 (57.1%)	6 (35.3%)	66 (60.6%)	0.05
Liquid	54 (42.9%)	11 (64.7%)	43 (39.4%)	
ANC1, mean ± SD	5725.5 ± 4906.3	7559.5 ± 8033.6	5439.4 ±4205.7	0.301

Note: 1ANC: Absolute Neutrophilic Count, reported as mean ± standard deviation (SD).

Urine analysis results

UA was positive in 13.0% of all patients. Leukocyte Esterase (LE) and bacteria were both positive in 7.4% of the urine samples obtained. Nitrite and White Blood Cells (WBCs) were positive in 1% and 2.7% of the samples, respectively. A positive UC was significantly associated with a positive UA compared to a negative UC (44.8% vs. 9.6%, p<0.001). Paradoxically, patients with a positive UC were more likely to have a negative UA than having a positive UA (55.2% vs. 44.8%). Furthermore, in patients with a positive UA, as high as 66.7% (26/39) had a negative UC ultimately, with only 33.3% (13/39) later found to have a positive UC. Patients with a positive UC had significantly more positive UA findings of LE31.0% vs. 4.9%; p<0.001), nitrite (6.9% vs. 0.4%, p=0.026), and bacteria (31.0% vs. 4.9%, p<0.001) than those with a negative UC. There was no significant difference between the two groups in the UA finding of WBCs (Table 3a).

Table 3a: Urine analysis results in patients with positive vs. negative UC.

Variables, n (%)	All patients N=301 (100%)	Positive UC	Negative UC	P-value
		n=29 (9.6%)	n=272 (90.4%)	
Leukocyte Esterase (LE)				
Positive	22 (7.4%)	9 (31.0%)	13 (4.9%)	<0.001
Negative	274(95.6%)	20(69.0%)	254(95.1%)	
Nitrite				
Positive	3 (1%)	2 (6.9%)	1 (0.4%)	0.026
Negative	293 (99%)	27(93.1%)	266(99.6%)	
WBCs[1]				
Positive	8 (2.7%)	2 (6.9%)	6 (2.2%)	0.179
Negative	288(97.3%)	27(93.1%)	261(97.8%)	
Bacteria				
Positive	22 (7.4%)	9 (31.0%)	13 (4.9%)	<0.001
Negative	274(92.6%)	20(69.0%)	254(95.1%)	
Urine analysis[2]				
Positive	39 (13.0 %)	13(44.8%)	26 (9.6%)	<0.001
Negative	262(87.0%)	16(55.2%)	246(90.4%)	

Note: [1]WBCs: White Blood Cells, considered positive if ≥ 5 WBC/HPF (i.e., pyuria) [2]. Urine analysis was considered positive if any of the above findings were positive.

In FN patients, UA was positive in 10.9% of the samples and UC was positive in 6.9% of patients only. LE and bacteria were positive in 5.3% and 7.6%, respectively. None of the samples obtained from neutropenic patients was positive for WBCs. Nitrite was positive in 1.2% of samples obtained from neutropenic patients (Table 3b).

Table 3b: Urine analysis results in FN patients with positive vs. negative UC.

Variables, n (%)	All FN patients N=175 (100%)	Positive UC n=12 (6.9%)	Negative UC n=163 (93.1%)	P-value
Leukocyte Esterase (LE)				
Positive	9 (5.3%)	4 (33.3%)	5 (3.1%)	<0.001
Negative	162(94.7%)	8 (66.7%)	154(96.9%)	
Nitrite				
Positive	2 (1.2%)	1 (8.3%)	1 (0.6%)	0.136
Negative	169(98.8%)	11(91.7%)	158(99.4%)	
WBCs[1]				
Positive	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Negative	171(100.0%)	12(100.0%)	159 (100.0%)	
Bacteria				
Positive	13 (7.6%)	4 (33.3%)	9 (5.7%)	<0.001
Negative	158 (92.4%)	8 (66.7%)	150(94.3%)	
Urine Analysis[2]				
Positive	19 (10.9%)	6 (50.0%)	13 (8.0%)	<0.001
Negative	156 (89.1%)	6 (50.0%)	150(92.0%)	

Note: [1]WBCs: White Blood Cells, considered positive if ≥ 5 WBC/HPF (i.e., pyuria).
[2]2 Urine analysis was considered positive if any of the above findings were positive.

Analyzing the FN subgroup of the studied population, a positive UC was significantly associated with a positive UA, compared to those with a negative UC (50% vs. 8%, p<0.001). Although statistically significant, it is important to mention that while half of FN patients with a positive UC also had a positive UA result, the other half had a negative UA. In other words, a smaller percentage of FN patients with a positive UA had a concomitantly positive UC, while the vast majority had a negative UC (6/19=31.6% vs. 13/19=68.4%). Moreover, a positive UC in these neutropenic patients was significantly associated with positive UA findings of LE and bacteria (p=0.001 and p=0.007, respectively) (Table 3b).

In non-neutropenic patients, on the other hand, UA was positive in 15.9% and UC was positive in 13.5% of patients. LE and bacteria were positive in 10.3% and 7.2%, respectively. WBCs were positive in 6.4% and nitrite was positive in 0.8% of samples (Table 3c).

In non-FN patients, like neutropenic patients, a positive UC was significantly associated with a positive UA, compared to those with a negative UC (41.2% vs. 11.9%, p=0.006). Only 41.2% of the patients with a positive UC also had a positive UA result, whereas the majority (58.8%) had a negative UA. Most non-FN patients (13/20=65%) with a positive UA had a negative UC, in comparison to 35% (7/20) that had both, UA and UC, positive. A positive UC in non-FN was significantly associated with positive UA findings of LE and bacteria (p=0.017 and p=0.002, respectively) (Table 3c).

Diagnostic performance of urine analysis findings

In our study, a UA was found to be 44.8% sensitive, 90.4% specific and 86.1% accurate for the diagnosis of a UTI in febrile pediatric patients with cancer, with a Positive Predictive Value (PPV) of 33.3% and a Negative Predictive Value (NPV) of 93.9%. Additionally, none of the UA components was strongly sensitive, nor did any have a strong PPV. Specificity, NPV and accuracy of all these tested components, on the other hand, were high. Furthermore, the sensitivity and specificity did not significantly differ in patients with or without neutropenia (Table 4).

Table 3c: Urine analysis results in non-FN patients with positive vs. negative UC.

Variables, n (%)	All non-FN patients N=126 (100.0%)	Positive UC n=17 (13.5%)	Negative UC n=109 (86.5%)	P-value
Leukocyte Esterase (LE)				
Positive	13 (10.3%)	5 (29.4%)	8 (7.3%)	0.017
Negative	112 (89.6%)	12 (70.6%)	100(92.6%)	
Nitrite				
Positive	1 (0.8%)	1 (5.9%)	0 (0.0%)	0.136
Negative	124 (99.2%)	16 (94.1%)	108 (100.0%)	
WBCs[1]				
Positive	8 (6.4%)	2 (11.8%)	6 (5.6%)	0.298
Negative	117 (93.6%)	15 (88.2%)	102(94.4%)	
Bacteria				
Positive	9 (7.2%)	5 (29.4%)	4 (3.7%)	0.002
Negative	116 (92.8%)	12 (70.6%)	104(96.3%)	
Urine analysis[2]				
Positive	20 (15.9%)	7 (41.2%)	13 (11.9%)	0.006
Negative	106 (84.1%)	10 (58.8%)	96 (88.1%)	

Note: [1] WBCs: White Blood Cells, considered positive if ≥ 5 WBC/HPF (i.e., pyuria). [2] Urine analysis was considered positive if any of the above findings were positive.

Table 4: Diagnostic performance of urine analysis findings.

Variable	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
For all febrile cancer patients (N=301)					
Leukocyte Esterase (LE)	31.03% (15.3%-50.8%)	95.10%	40.90%	92.7% (90.6%-	88.9% (84.7%-
Nitrites	6.90%	99.60%	66.70%	90.8% (89.9%-	90.5% (86.6%-
WBCs[1]	6.90%	97.80%	25% (6.6%-	90.6% (89.7%-	88.9% (84.7%-
Bacteria	31.00%	95.10%	40.90%	92.7% (90.9%-	88.85% (84.7%-
Urine Analysis[2]	44.80%	90.40%	33.30%	93.9% (91.7%-	86.1% (81.6%-
For FN cancer patients (N=175)					
Leukocyte Esterase (LE)	33.30%(9.9%-65.1%)	96.90%(92.8%-98.97%)	44.40%(19.8%-72.2%)	95.1% (92.8%-96.6%)	92.4% (87.4%-95.9%)
Nitrites	8.30%(0.2%-38.5%)	99.40%(96.6%-99.98%)	50% (6.2%-93.8%)	93.5% (92.4%-94.5%)	92.98% (88.1%-96.3%)
WBCs1	0.00%(0.0%-26.5%)	100.00%(97.7%-100.0%)		92.98%(92.98%-92.98%)	92.98% (88.1%-96.3%)
Bacteria	33.30%(9.9%-65.1%)	94.30%(89.5%-97.4%)	30.80%(13.8%-55.2%)	94.9% (92.6%-96.6%)	90.1% (84.6%-94.1%)
Urine Analysis[2]	50%(21.1%-78.9%)	92.00%(86.8%-95.7%)	31.60%(17.6%-49.9%)	96.2% (93.4%-97.8%)	89.1% (83.6%-93.3%)
For non-FM cancer patients (N=126)					
Leukocyte Esterase (LE)	29.40%(10.3%-55.96%)	92.60%(85.9%-96.8%)	38.50%(18.8%-62.8%)	89.3% (85.9%-91.9%)	84% (76.4%-89.9%)

Nitrites	5.90%(0.2%-28.7%)	100.00%(96.6%-100.0%)	100.00%	87.1% (85.7%-88.4%)	87.2% (80.1%-92.5%)
WBCs[1]	11.80%(1.5%-36.4%)	94.40%(88.3%-97.9%)	25.00%(6.8%-60.3%)	87.2% (85.0%-89.1%)	83.2% (75.5%-89.3%)
Bacteria	29.40%(10.3%-55.96%)	96.30%(90.8%-98.98%)	55.60%(27.1%-80.8%)	89.7% (86.4%-92.2%)	87.2% (80.1%-92.5%)
Urine analysis[2]	41.20%(18.4%-67.1%)	88.10%(80.5%-93.5%)	35% (20.1%-53.6%)	90.6% (86.5%-93.5%)	81.8% (73.9%-88.1%)

[1] WBCs: White Blood Cells, considered positive if ≥ 5 WBC/HPF (i.e., pyuria).
[2] Urine analysis was considered positive if any of the above findings were positive.

DISCUSSION

In our study, around ten percent of all febrile pediatric cancer patients were found to have a positive UC. This finding of ours is in line with findings from other studies showing a UTI prevalence varying between 10% to 26% in FN patients [19]. Such a percentage should not be taken lightly. In fact, it enforces the need for having a high index of suspicion for UTIs in such a vulnerable population, especially in the absence of a clear clinical picture.

Our results are also congruent with findings from the general population, where the prevalence of UTIs is significantly higher in females compared to their male counterparts [20]. This has also been reported by Montini et al. in a study conducted on pediatric FN patients, wherein the authors report a higher rate of UTIs in girls than in boys over the first 8 years of life (8% vs. 2%, respectively) [21]. Comparable results showing a predominance of UTIs in females have also been reported when studying adult FN patients [16,22,23]. According to Li et al., female gender is considered an additive risk factor for developing genitourinary tract infections (OR 3.52; 95%CI [1.74–7.12]; p<0.001) [24]. Authors have explained this by the fact that girls are more likely to postpone voiding compared to boys, and since infrequent voiding was shown to be a risk factor for febrile UTIs, this can explain the finding of sex as an independent predictor of UTIs [25].

Febrile patients with cancer are heterogeneous in terms of susceptibility to infections, due to several factors, including but not limited to, the underlying tumor type and stage, chemotherapeutic regimens received, comorbidities, previous history of infections (particularly resistant organisms) ...etc. [26]. In our study, patients with a positive UC were more likely to have liquid rather than solid tumors. This was also shown by Galvis et al. who reported that as high as 94.3% of the UTI episodes corresponded to lymphoid or myeloid leukemia's [19]. Interestingly, this finding contradicts with a similar study we conducted on adult FN cancer patients, wherein those with solid tumors were more likely to develop a UTI [23]. It also clashes with the results of Hirmas et al. who found that UTIs, particularly those associated with the isolation of resistant gram-negative bacteria from a UC, were more significantly seen in patients with solid tumors [12]. In her paper around the epidemiology of infections in cancer patients, Zembower explains that the risk of infection in patients with solid tumors is not the same as that in those with underlying hematological malignancies, and attributes this to the fact that the standard chemotherapeutic agents used to treat solid malignancies do not lead to long-term, nor to profound neutropenia [27]. Nevertheless, there remains an exception to every rule, and sometimes, solid tumors are a major risk factor for contracting infections, either because of using aggressive chemotherapeutic agents (like in some sarcomas and testicular carcinomas), or in cases where the expanding tumor damages normal anatomical barriers (which can be seen in tumors of skin, urogenital, respiratory, and gastrointestinal tracts) [27].

The results of a UA are obtained through biochemical analyses of LE and nitrite via a rapid dipstick method, as well as urine microscopic examination for pyuria (WBCs) and bacteriuria (i.e., bacteria in urine) [28]. Our results regarding the diagnostic validity of UA components go in parallel with the findings of Hirmas et al. who concluded that there is limited sensitivity of pyuria, LE and nitrite in detecting UTIs in the setting of cancer, namely in neutropenic patients [12]. This was also reinforced by Klaassen et al., who reiterated the absence of pyuria in pediatric cancer patients with a UTI and reported that pyuria was detected in as low as four percent of the UTI episodes during neutropenia, in comparison to 68.0% in non-neutropenic controls (p<0.0001) [5]. Likewise, Sandoval et al. reported a low sensitivity of pyuria in neutropenic patients, such that it was identified in 4.3% (1/23) of neutropenic UTIs and 67.7% (21/31) of non-neutropenic UTIs (p<0.0001) [16].

Three pediatric meta-analyses and two studies, all of which were conducted on previously healthy children, reported LE sensitivities of 72%-86% [9]. This comes to contradict with the results of our study, conducted on pediatric oncology patients, that showed a very low LE sensitivity. This is largely explained by the lack of adequate inflammatory response to bacterial infiltration, together with the leukopenia found in many of these patients, which limits the number of leukocytes available for excretion in the urine, even in the presence of a local infection [5,16].

In their review article on the diagnosis of UTIs in pediatric patients, Tsai et al. state that nitrite has a low sensitivity of 50% (i.e., high false negatives) but a high specificity of 98% (i.e., low false positives) for the detection of pediatric UTIs [27]. The authors clarified this result by two facts. Firstly, not all organisms causing UTIs produce nitrites like Pseudomonas aeruginosa and most gram-positive organisms. Second, it requires a minimum of four hours for dietary nitrates to convert into nitrites by a uropathogen in the bladder [28,29]. Consequently, false negatives may occur in children who void frequently [28]. Another reason for a false negative result can be the use of antibiotics that inhibit bacterial metabolism [29].

Overall, our numbers (UA sensitivity of 44.8%, specificity of 90.4% and an NPV of 93.9%) matched those of Sandoval et al., who documented a sensitivity of 40%, specificity of 94% and an NPV of 94% for a UA in the diagnosis of a UTI [16]. Our findings are also in line with those of Galvis et al. who found a low sensitivity for all UA components, with greater specificity and NPV for all components alone or combined, with a better performance for nitrite [15], which we have proven to be the most specific in our study (99.6% specificity in all febrile pediatric oncology patients, 99.4% in FN patients, and 100% in non-FN patients). These results of ours were strongly corroborated in the literature. In fact, the authors of several studies deemed a UA an insufficient

diagnostic tool to rule a UTI in or out, mainly during the period of neutropenia [16,19]. This brings us to the conclusion that recommendations suggesting a pivotal role of UA in the workup of febrile pediatric cancer patients must be thoroughly revised.

The IDSA states that a routine UC frequently yields clinically irrelevant information [15]. As per its guidelines, a UC is only warranted if the patient has urinary signs and symptoms, a foley catheter, or positive UA findings [12,15]. In a prospective study by Sandoval et al., which sought to determine the frequency of UTIs in pediatric cancer patients with FN, the authors refuted IDSA's statement because none of their patients with a UTI presented with urinary symptoms and only one had WBCs on UA [16]. This is consistent with the fact that fever can often be the only sign of a serious underlying infection due to severe impairment of cancer patients' immune system [30].

We find ourselves inclined to agree with Sandoval et al. In our paper, we have shown that all febrile pediatric cancer patients (FN and non-FN) who were found to have a positive UC were initially found to have a negative, rather than a positive UA (55.2% vs. 44.8%). Upon further stratifying our patient population into FN vs. non-FN, we found that half of FN patients with a positive UC, and the larger part of non-FN patients with a positive UC had a negative UA on presentation (58.8% vs. 41.8%). In other words, 66.7% of all pediatric cancer patients (including FN and non-FN), 68.4% of FN patients, and 65% of non-FN patients, presenting to the ED with fever and found to have a positive UA, ultimately had negative UC.

This is of utmost importance, because in such situations, had we relied on a UA alone, many lives would have been endangered. If we chose to withhold antibiotics solely based on a negative UA, we would have increased the risk of severe infections and thus morbidity and mortality rates. On the other hand, had we initiated treatment based on a positive UA without obtaining a UC, which is the known gold standard with a sensitivity reaching 95% and specificity of up to 99%, to confirm the infection, isolate the organism, and test for susceptibilities, we would have over treated many patients increasing the risk of antibiotics resistance and missed many resistant and life-threatening organisms that could have been identified and adequately targeted with the optimal antibiotics.

This comes to prove that we cannot fully rely on a UA to rule in or out a UTI in this population. It also confirms what was concluded by Hirmas et al., who have demonstrated that a positive UC in pediatric cancer patients may not be associated with UA abnormalities, particularly in the setting of neutropenia [12]. Bearing this in mind, we believe it is rather lifesaving to revisit the IDSA guidelines regarding obtaining a UC in febrile pediatric cancer patients presenting with fever, even in the absence of urinary signs or symptoms, mainly in neutropenic children, as a UA has repeatedly proven to be a weak diagnostic tool.

CONCLUSION

In conclusion, a UC showing ≥ 100,000 CFU/ml remains the gold standard and the mainstay for the diagnosis of a UTI in the general population and in febrile pediatric cancer patients, especially if neutropenic, even in the absence of localizing urinary signs and symptoms. Although simple, quick, cheap, and readily available, a UA is of poor value in making an absolute diagnosis, when compared to a UC. Therefore, we recommend coupling a urine analysis with a urine culture as part of the routine workup in all pediatric cancer patients presenting with fever, after which immediate empirical antibiotics should be initiated, to be later tailored based to the results of the culture. In a population as ours, vulnerable, immunosuppressed, and fragile, it is compulsory to keep one step ahead and to stay on your toes. It is rather lifesaving to prevent an infection or to treat it as early as a diagnosis is made, with the intention of preventing its progression, decreasing morbidity and mortality rates, and improving the overall quality of life of these patents.

LIMITATIONS

It should be noted that this study has some limitations. The results of this study are from a single tertiary academic center with a relatively small sample size (among the 301 included participants, only 9.6% (29 patients) had a positive UC). Still, AUBMC is one of the major referral centers in Lebanon and the Middle East, and its ED is one of the busiest in the region, which renders our patient population adequately representative of the general population and enforces the external validity of our paper. Moreover, given the retrospective nature of our study, the research team faced issues like resource restrictions and data unavailability during data collection (mainly upon retrieving data from the scanned hand-written charts). This was overcome by following a unified data collection manual that was repeatedly adjusted after a pilot data collection. A quality check after 50% of the records were collected was done as means to improve the process of data collection.

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The authors declare that they have no conflicts of interest to disclose.

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All authors have contributed equally to this work.

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