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Patterns of microbial growth in urine cultures in a pediatric hematology/oncology unit over a one-year period: a single institution study

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ABSTRACT

Background: Urinary tract infections (UTIs) may present with nonspecific symptoms and without any definitive clinical signs other than fever, hence may be missed without a routine urine analysis. We retrospectively evaluated all cases of culture-positive urine infections in pediatric oncology patients in our center during the year 2015.

Methods: We assessed all positive urine culture incidents for pediatric patients receiving treatment and/or follow-up at our center during 2015. Analysis was performed on patients with regards to clinical, microbiology and pertinent lab findings as well as associated risk factors.

Results: There were 151 episodes of documented positive urine cultures among 73 patients. Majority of positive urine cultures were found in solid tumor patients (41%), followed by hematological malignancies (26%). Most organisms detected were gram-negative organisms (84%), with *E.coli* being the most frequent (51%). Forty percent of bacteria were resistant to standard broad-spectrum antibiotics, with the majority being extended-spectrum beta-lactamase-producing. Most of these infections occurred in patients receiving prophylactic antibiotics (46 out of 50). Approximately two thirds of patients were not febrile on the day of culture (64%) and almost half of the reported episodes were associated with urinary symptoms. Pyuria, leukocyte esterase and nitrites were positive in 39%, 51% and 19% of samples, respectively.

Conclusions: Positive urine culture in children with cancer may not be associated with urinalysis abnormalities, particularly in patients with neutropenia. When selecting empiric treatment for cancer patients with UTIs, one should take into consideration the institutional patterns for resistance and use of prophylactic antibiotics.

1. Introduction

Cytotoxic drugs are the basis of treatment for patients with malignant disease. The development of neutropenia is commonly a side effect of chemotherapy and increases the risk of serious bacterial infections. Even though this is usually offset by the use of colony stimulating factors and prophylactic antibiotics, the incidence of infections in such patients remains high [1]. Of even greater interest is the situation encountered when treating pediatric patients who, especially in our part of the world, often present a unique subset because of their own risks and management problems.

Unlike acute respiratory or gastrointestinal tract infections, urinary tract infections (UTIs) may present with nonspecific symptoms and without any definitive clinical signs other than fever [2]. The diagnosis of UTI may be missed unless urine cultures are routinely obtained. UTIs in pediatric cancer patients in the setting of febrile neutropenia has not been well studied.

This study retrospectively evaluates all cases of culture-positive urine infections in pediatric oncology patients at King Hussein Cancer Center during the year 2015.

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Abbreviations

ESBL	Extended-spectrum beta-lactamase
GU	Genitourinary
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
TMP-SMZ	Trimethoprim-sulfamethoxazole
UTI	Urinary tract infection

2. Materials and methods

This study was approved by the Institutional Review Board at the King Hussein Cancer Center in Amman, Jordan. All positive urine cultures were recorded and archived in the Infection Control Unit at our center. Inclusion criteria included pediatric patients (<18 years of age at diagnosis) who were treated at the center, either as inpatient or outpatient, and had a positive urine culture between January 1, 2015 until December 31, 2015.

Data was collected from the Infection Control Unit with regards to pathogen type and sensitivity/resistance patterns. Resistance patterns were documented according to the MDRO/CDI module (Multidrug-Resistant Organism & *Clostridium difficile* Infection) [3]. This module provides a mechanism for facilities to report and analyze infection data in line with Healthcare Infection Control Practices Advisory Committee (HICPAC) guidelines for the control of multidrug-resistant organisms and *Clostridium difficile*.

Digital patient records were accessed to acquire the following information: patient demographics, total number of positive urine cultures per patient, admission dates, urine analysis and culture details, blood culture results, complete blood count (CBC) findings as well as pertinent risk factors including intensive care unit (ICU) stay, post-op infection, presence of Foley catheter, tubes or stents, and presence of congenital or anatomic abnormalities in the genitourinary (GU) tract including malignancies. According to our unit's clinical practice guidelines, free urine samples for analysis and culture are usually collected by clean-catch mid-stream urine or via catheterization done under sterile conditions.

Statistical analysis was done using MedCalc software [4] for data management and analyses. Fisher's exact test was used to assess the significance of concomitance of the following pairs: positive leukocyte esterase and pyuria, positive leukocyte esterase and neutropenia, positive nitrites and pyuria, and positive nitrites and neutropenia.

3. Results

3.1. Sample and patient characteristics

There were 151 episodes of documented positive urine culture retrieved from our database at the Infection Control Unit (Table 1). These samples represented 73 patients who were identified using medical record numbers. Male-to-female ratio was 1:5. The majority of positive cultures were for solid tumor patients (N = 62, 41%), including germ-cell (N = 11) and gonadal tumors (N = 14), followed by 26% (N = 39) of episodes in hematological malignancies, brain tumors in 9% (N = 14) and the remaining 24% (N = 36) of episodes in non-cancer related cases: Thalassemia, autoimmune hemolytic anemia, Fanconi anemia, neurofibromatosis type 1, severe combined immunodeficiency and sickle cell disease. Twelve patients out of the 73 had associated genitourinary cancers (16%).

The majority of samples (85%) were obtained in patients with neutrophil count exceeding 500 cells/μL; while only 13 (9%) had neutropenia at time of sample collection. Only one quarter of samples (26%, N = 39) were collected at time of fever. Sixty-five samples (43%) had associated urinary symptoms at time of sampling. There was a median of 3 positive urine cultures per patient (range, 1–23). The majority of urine samples were procured freely (N = 112, 74% of cultures) and Foley catheter was used in (N = 4) 3% of cultures. The remaining three methods involved one patient each: urostomy tube in 15% of cultures, vesicostomy in 4% and condom catheter in 4%. Follow-up culture was a series of positives in 49 episodes (32%).

Forty-nine urine cultures (32% of cultures) belonging to 12 patients (16% of patients) were part of a series of positive urine cultures. Per patient, the median percentage of positive cultures as part of a series is 33% (range, 4–100%) of all positive cultures for each patient, and the median is one series of positives for each patient (range, 1–6). Median days from initial positive culture to the first negative culture in each series is 21 days (range, 2–143 days) per patient. Urine was procured freely in 9 patients, and in the remaining patients, vesicostomy tube, condom catheter and urostomy tube were involved individually.

3.2. Co-morbidities

ICU stay was associated with 9 episodes (6%), UTI was a postoperative infection in 3 episodes (2%), and concomitant GU anatomic abnormalities were found in 63 episodes (42%). These anatomic abnormalities included associated GU malignancies, any tumor impinging on urinary bladder, history of nephrectomy or scarred kidney, as well as use of instrumentation at time of urine culture (Foley and condom catheters, nephrostomy and

Table 1
Characteristics of patients and positive urine cultures in our study.

	Number of patients (%)	Number of episodes (%)
Total	**73**	**151**
Gender		
Male	12 (16%)	27 (18%)
Female	61 (84%)	124 (82%)
Cancer type		
Hematologic	21 (29%)	39 (26%)
Solid	28 (38%)	62 (41%)
Brain tumors	14 (19%)	14 (9%)
Other	10 (14%)	36 (24%)
Associated GU Cancer	12 (16%)	31 (21%)
Site of urine procurement		
Free		112 (74%)
Foley catheter		4 (3%)
Urostomy		23 (15%)
Vesicostomy		6 (4%)
Condom catheter		6 (4%)
Colony Count (CFU)		
Unknown		2 (1%)
10,000 to 99,000		32 (21%)
≥100,000		117 (78%)
ANC (cells/uL)		
Unknown		9 (6%)
≤500		13 (9%)
>500		129 (85%)
Patient febrile on day of culture		
No documentation		15 (10%)
Yes		39 (26%)
No		97 (64%)
Patient had urinary symptoms on day of culture		
No documentation		15 (10%)
Yes		65 (43%)
No		71 (47%)

vesicostomy tubes or stents, and double J stents).

3.3. Urine analysis findings

Urine analysis was documented in 142 out of 151 (98%) episodes. Urine abnormalities were reported in association with 98 out of the 142 (69%) documented available urine analysis samples. Pyuria and leukocyte esterase were reported in 39% (N = 56) and 51% (N = 73) of all samples. Samples associated with neutropenia had pyuria and positive leukocyte esterase in 15% and 23%, respectively. Leukocyte esterase was strongly associated with pyuria ($P < 0.001$). On the other hand, nitrite test was positive in 19% of samples (N = 27) and was strongly associated with pyuria ($P < 0.001$).

3.4. Organism types and patterns of resistance

The majority of organisms detected by urine culture were gram-negative organisms (84%), with *E.coli* being the most frequent organism (51%), followed by *K.pneumonia* (9%) and *P.aeruginosa* (8%). 37% of gram-negative organisms were extended spectrum beta-lactamase (ESBL)-producing and 3% were multi-drug resistant (total 40%), indicating resistance to standard antibiotics. Most common gram-positive bacteria detected were coagulase-negative *Staphylococci* (6.6%) and *Enterococci* (5%). There were no vancomycin-resistant enterococci or methicillin-resistant Staphylococci detected, hence gram-positive bacteria were generally sensitive to standard antibiotics. Sensitivity patterns of gram-negative and gram-positive organisms are summarized in Figs. 1 and 2, respectively.

Resistant gram-negative bacteria (N = 50) were most commonly reported in patients with solid tumors (N = 21, 17%). Fourteen samples were documented in patients with associated GU cancer (11%) and 10 cultures (8%) were associated with nephrostomy tubes. Only 4 (3%) of these cultures were reported in patients who were on prophylaxis (Table 2).

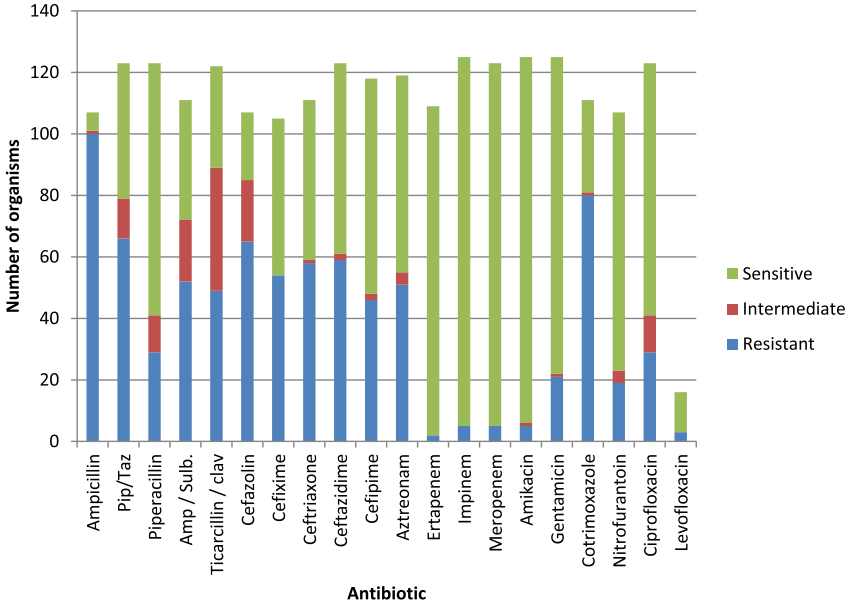

Fig. 1. Sensitivity testing for gram-negative organisms.

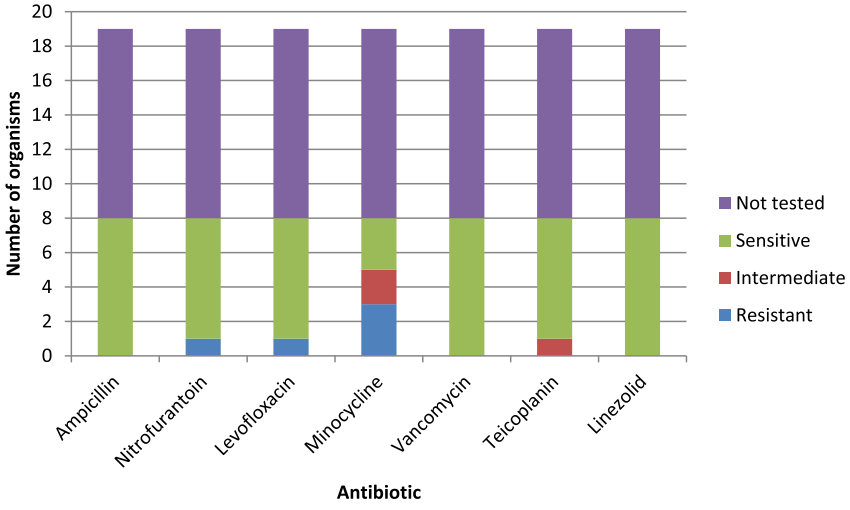

Fig. 2. Sensitivity testing for gram-positive organisms.

Table 2
Percentage of ESBL-Producing and Multidrug Resistant Gram-Negative Bacteria in Urine Cultures.

	Resistant organisms N (% from total gram-negative bacteria, N = 126)
Total	50 (40%)
By cancer type	
Brain	4 (3%)
Hematologic	12 (10%)
Solid	21 (17%)
Others	13 (10%)
By genitourinary abnormality	
No abnormality	42 (33%)
Bleeding and enlarged vaginal tumor	2 (2%)
Tumor impinging on urinary bladder	1 (1%)
Right nephrectomy, scarred left kidney	5 (4%)
Associated GU cancers	14 (11%)
Instruments	
Foley catheter	2 (2%)
Condom catheter	1 (1%)
Nephrostomy tube/stent	10 (8%)
Vesicostomy tube	4 (3%)
Double J stent	1 (1%)
By use of prophylactic antibiotics	
Yes	4 (3%)
No	46 (37%)

4. Discussion

We have looked at the growth patterns in urine cultures for all pediatric oncology patients receiving treatment and/or follow-up at our center for a one-year period. Our unit is an intermediate-sized unit with approximately 300 new patients admitted annually. As can be seen from the results, the majority of organisms causing UTI's are gram-negatives with *E.coli* being the most frequent organism, a finding commonly reported in the literature [2,5]. 40% of the gram-negative organisms were found to be resistant, and among the *E.coli* species recovered, 53% were ESBL-producing organisms. This is consistent with our hospital antibiogram as almost half of our gram-negative isolates were resistant to third generation cephalosporins.

Positive urine cultures were more likely to be found in patients with solid tumors (39%). Also, 42% of patients had genitourinary abnormalities as defined previously; these patients were more likely to have frequent positive urine cultures. It is noticed from our findings that patients who had urinary instruments (like nephrostomy tubes or Foley catheters), those who had persistent infections and those with congenital or acquired GU anomalies underwent more frequent urine culturing, but were not necessarily placed on prophylactic antibiotic treatment compared to their counterparts.

In our series, only 4 episodes (each belonging to a separate patient) were associated with positive blood cultures, two of which had the same organism found in urine culture. Three of these 4 patients were females, and only 1 was an oncology patient who ultimately developed urosepsis and septic shock.

A prospective study on the clinical relevance of the urinary tract as a source of infection [2] showed that 8.6% of pediatric oncology patients with febrile neutropenia had a UTI, most common organism being *E.coli*. In comparison, 6.9% of patients had bacteremia. The majority of the patients with UTI were girls, each patient except for one was receiving TMP-SMZ, and the one male patient with UTI was circumcised. They also observed that the *E. coli* isolated was resistant to TMP-SMZ and the only patient not receiving TMP-SMZ developed a UTI with a TMP-SMZ sensitive organism.

Munyi et al. studied the prevalence of UTI in 186 pediatric patients with leukemia or lymphoma [5]. Fifteen patients (8.1%) had UTI, with the most common organism being *E. coli* ($n = 10$). In this study, UTI was defined as the presence of >100 cfu/mL; also, the circumcision status of their male patients and whether patients were receiving prophylactic antibiotics were not reported. *Al-Bahar et al.* studied 100 consecutive Kuwaiti adult and pediatric patients with febrile neutropenia [6]. Thirteen patients had UTI. Ten of these UTIs occurred in women and 8 patients were not receiving oral prophylactic antibiotics.

The Infectious Diseases Society of America (IDSA) guidelines state that sending urine cultures is indicated if signs or symptoms of UTI exist, a urinary catheter is in place, or the urinalysis is abnormal [7]. Moreover, IDSA states that routine culture of urine yields clinically irrelevant information. However, *Klaassen et al.* reported on the absence of pyuria in neutropenic pediatric oncology patients with UTI [8]. Pyuria was detected in 1 of 23 neutropenic episodes of UTI compared to 21/31 non-neutropenic episodes ($P < 0.0001$). This is also evident in our findings (Table 3) where pyuria was detected in 2 out of 13 neutropenic episodes (15%) compared to 50 out of 120 non-neutropenic episodes (42%) ($P = 0.078$). Moreover, nitrite testing in younger children (without cancer) is also less effective than in older patients [9,10]. From our findings, it is apparent that there is limited sensitivity of pyuria, leukocyte esterase and nitrite test in detecting UTI in the setting of cancer, particularly in neutropenic patients. It is also worth noting that patients with neutropenia may not have been sampled when urinary symptoms were absent. Finally, UTIs may be the initial warning of the presence of a urinary tract anomaly, and recurrent UTIs can contribute to scarring, which may lead to hypertension and renal failure [2].

Hence, given the concerns with delayed therapy and risk of potential adverse events with invasive urine collection, it is recommended [10] that clean-catch or mid-stream urine samples be collected before starting antibiotics, but this should not delay treatment.

Table 3
Neutrophil count in relation to pyuria in 133 documented samples.[a]

	ANC ≤ 500	ANC > 500	Total
Pyuria (urine WBC ≥5)	2 (15%)	50 (42%)	52 (39%)
No pyuria	11 (85%)	70 (58%)	81 (61%)
Total	13 (100%)	120 (100%)	133 (100%)

[a] Urinalysis was not taken in nine patients, and CBC was not performed in another nine patients.

5. Conclusions

Our study is limited by virtue of its retrospective nature; nevertheless, important conclusions can be made. Positive urine culture in children with cancer may not be associated with urinalysis abnormalities, particularly in patients with neutropenia. Resistant bacteria in urine reflect the pattern of resistance in the institution, with selection introduced by the use of prophylactic antibiotics which do not cover resistant bacteria.

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