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Original Article

Urinary Tract Infections in Pediatric Oncology Patients with Fever and Neutropenia

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Abstract

Background: The relevancy of the urinary tract as a source of infection during febrile neutropenia is still to be known. We sought to determine the frequency of urinary tract infections (UTIs) in pediatric cancer patients with febrile neutropenia. **Methods**: Urine was collected from a mid-stream void before the administration of antibiotics. Demographic, clinical, and laboratory data were collected. The frequency of UTI and usefulness of urinalysis and localizing signs in predicting UTI in pediatric cancer patients with fever and neutropenia were determined. **Results:** Forty-five patients who had 58 febrile neutropenic episodes were included in the study for participation. No patient presented with localizing signs. The urinalysis was negative in 53 episodes and positive in 5 episodes. Four patients had 5 UTIs. The frequency of UTI was 8.6% (5 of 58 febrile neutropenia episodes). Four patients had bacteremia, none of whom had a UTI. The sensitivity, specificity, and negative predictive value of urinalysis was 40%, 94%, and 94%, respectively, and for localizing signs was undefined, 100%, and 91%, respectively. **Conclusions:** UTI is as common as bacteremia in the current pediatric cancer patients with fever and neutropenia. Urinalysis and urine culture should be obtained routinely as part of the diagnostic evaluation of patients with fever and neutropenia.

Key words: Febrile neutropenia; Pediatric oncology; Urinary tract infection.

INTRODUCTION

Neutropenia is defined as an absolute neutrophil count of less than 500 cells/mm^3. It is a frequent consequence of chemotherapy and increases the risk of serious bacterial infections.[1] Although empiric therapy with broad-spectrum antibiotics is routinely instituted, selecting the most appropriate therapy depends upon the assessment of the infection based on the clinical picture. 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. Thus the diagnosis of UTI may be missed unless urine cultures are routinely obtained. The incidence of UTI in adult oncology patients with febrile neutropenia ranges from 5% to 30%[2–4]; however, the frequency of UTI in pediatric cancer patients with febrile neutropenia has not been well studied.

The prevalence of UTIs in African pediatric oncology patients is 8.1%.[5] However, in this study, the definition of UTI was growth of 100 or more colony-forming units (cfu)/mL and the circumcision status of the male patients were unknown. Therefore, the findings of this study may not be generalized. The preva-

lence of urinary tract infections range from 3.3% to 5.3% in otherwise normal infants and children presenting to our department for the evaluation of fever.[6,7] The use of the urine dipstick to detect leukocyte esterase and nitrites can be useful to screen children for the presence of a UTI. Negative results for these tests have a high predictive value. However, dipstick findings in a neutropenic patient may be difficult to interpret due to depressed inflammatory response and leukopenia may limit the numbers of white cells that are available to be excreted into the urine, and no rapid test (urine dipstick, a combination of dipstick and microscopy, enhanced urinalysis (UA)—white cell count per cubic millimeter plus gram stain, and gram stain alone) can detect all non-neutropenic infants with UTIs.[8]

We hypothesized that the urinary tract may be a common site of infection in paediatric oncology patients with fever and neutropenia, and prospectively studied this group of children for the presence of a UTI.

METHODS

Pediatric oncology patients with fever (temperature >38.5˚C on 1 measurement or >38˚C on 2 or more occasions during a 12-hour period) and neutropenia (absolute neutrophil count less than 500 cells/mm^3) were evaluated in the Department of Pediatric Haemato-Oncology, Bangabandhu Sheikh Mujib Medical University(BSMMU), Shahbag, Dhaka.

History and physical examination were performed. Blood cultures were obtained after sterilizing the skin with betadine. We allowed a 30-minute waiting period to collect urine before starting antibiotics unless the patient had signs of septic shock. Eligibility criteria included age range older than 2 years and younger than 14 years, cancer diagnosis receiving chemotherapy, febrile neutropenia, and parental, legal guardian, or patient written consent. Exclusion criteria included any patient who could not urinate on command or the use of intra-venous or oral antibiotics (except prophylactic trimethoprim-sulfamethoxazole [TMP-SMZ]) within the previous 2 weeks. Urine was collected from a mid-stream void and after cleaning and sterilizing the external genitalia with betadine. Urine was subjected to urinalysis (blood, bilirubin, urobilinogen, ketones, protein, nitrite, glucose, pH, specific gravity, and leukocytes) and culture. Routine bacteriologic, chemical, and microscopic techniques were used. A diagnosis of UTI was based on a positive urine culture defined as pure growth of a known urinary pathogen at >10^4 colony-forming units per milliliter (cfu/mL).

Demographic and clinical data comprised age, gender, circumcision status in boys, malignancy, current or most recent chemotherapy, use of prophylactic antibiotics and antifungal medications, any localizing symptoms (dysuria, hematuria, frequency), vital signs (temperature, blood pressure, pulse, and respiratory rate), empiric antibiotics, complete blood count with differential, serum chemistries, urinalysis results, blood culture results, and urine culture results.

All pediatric oncology patients presenting with fever (n = 55 patients over a 2-year period) were screened for study eligibility. Ten patients were deemed ineligible for the following reasons: 5 did not have a urinalysis sent, 3 had received antibiotics prior to obtaining a urine culture, 1 did not have a urine culture sent, and 1 did not give informed consent. Forty-five patients had 58 febrile neutropenic episodes eligible for study participation. Collection of urine for culture and urinalysis was necessary for study inclusion. Written informed consent was obtained from patients, parents, or legal guardians. The study was approved by the Institutional Review Board of the University. The sensitivity, specificity, and predictive values for the urinalysis and localizing symptoms were calculated, with a positive urine culture as the gold standard.

RESULTS

Thirty-three boys and 12 girls had a median age of 8 years (range, 2–14 years). Seventeen of the 33 boys were circumcised. Thirty-three patients had acute lymphoblastic leukemia, 11 had non-Hodgkin lymphoma, and 3 had acute myelogenous leukemia. No patient presented with dysuria, frequency, or hematuria. All patients were receiving pneumocystis jiroveci prophylaxis with TMP-SMZ except 1. The urinalysis was negative (no leukocyturia, negative nitrite, negative leukocyte esterase) in 53 episodes of febrile neutropenia and positive (>5 white cells/high-power field [hpf], and/or positive nitrite and/or positive leuko-cyte esterase) in 5, with the most common abnormality being the presence of leukocytes on microscopy (3 patients did not have a UTI and had 5 to 10 white cells/hpf). Four patients (3 girls and 1 circumcised boy) had 5 episodes of UTI (Table 1). One patient had 2 *Escherichia coli* infections (8 month interval between infections) and 1 had a single *E. coli* infection, 1 had vancomycin-resistant enterococcus (VRE) infection, and 1 had *Stenotrophomonas multiphila* infection. The *E. coli* and VRE organisms were resistant to TMP-SMZ and the patient with TMP-SMZ–sensitive *S. multiphila* was not

Table 1: Clinical features of patients with UTI

Patient	Age	Diagnosis	Circumcision Status	Urinalysis*	Organism	Sensitivity*
1	8 years	Osteosarcoma	NA	WBC 1–2/hpf	*E. coli*	Resistant
1	8 years	Osteosarcoma	NA	WBC 5–10/hpf	*E. coli*	Resistant
2	2 years	ALL	NA	Negative	*E. coli*	Resistant
3	16 years	Hodgkin disease	NA	Negative	VRE	Resistant
4	16 years	GBM	Yes	Negative	*S. multiphila*	Sensitive

Note: ALL = acute lymphoblastic leukemia; GBM = glioblastoma; multiforme; NA = not applicable; VRE = vancomycin-resistant enterococcus.
*Abnormal for non-neutropenic patients if >5–10/high-power field and sensitivity to TMP-SMZ.

taking TMP-SMZ after recovering from autologous stem cell rescue for recurrent brain tumor. The frequency of UTI in our patient population was 8.6% (5 infections out of 58 febrile neutropenic episodes). Four patients had bacteremia, none of whom had a UTI. The sensitivity, specificity, and negative predictive value of the presence of localizing signs was undefined, 100% and 91%, respectively, and for urinalysis was 40%, 94%, and 94%, respectively.

DISCUSSION

Our prospective study on the clinical relevance of the urinary tract as a source of infection showed that 8.6% of pediatric oncology patients with febrile neutropenia had a UTI. In comparison, 6.9% of patients had bacteraemia.

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). Sensitivity to TMP-SMZ was not assayed. However, this study has limitations that may make it difficult to generalize the findings. For instance, they defined UTI as the presence of >100 cfu/mL, whereas the accepted definition is >10,000 colony-forming units of a single organism per millimeter. 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.[2] Thirteen patients had UTI. Ten of these UTIs occurred in women and 8 patients were not receiving oral prophylactic antibiotics. Hamzeh et al. studied 64 adult patients with febrile neutropenia.[3] Seven patients had UTI, with *E. coli* isolated in 6 cases. These authors did not report whether patients were receiving prophylactic antibiotics. In our study, the majority of the patients with UTI were girls, each patient except 1 was receiving TMP-SMZ, and the 1 male with UTI was circumcised.

Reports on the risk of infection in pediatric patients with febrile neutropenia have included data on UTI.[9–12] However, these studies are limited by the following: 2 were retrospective, 3 did not define UTI and 1 used an unconventional definition, and none provided details on how urine was collected or the presence of symptoms. In these studies, the frequency of UTI ranged from 1% to 10%, and in 1 study of *E. coli* was the most common organism, as in our study.

The Infectious Diseases Society of America (IDSA) guidelines states that sending urine cultures is indicated if signs or symptoms of UTI exist, a urinary catheter is in place, or the urinalysis is abnormal.[13] Moreover, IDSA states that routine culture of urine yields clinically irrelevant information. Our prospective data refute the former statement because none of our patients with UTI presented with urinary tract symptoms and only 1 had the presence of leukocytes (5–10/hpf) on urinalysis. Klaassen et al. reported the absence of pyuria in pediatric oncology patients with UTI.[14] Pyuria was detected in 1 of 23 neutropenic episodes of UTI compared to 21/31 non-neutropenic episodes ($P < 0.0001$). UTIs may be the sentinel event of the presence of a urinary tract anomaly, and recurrent UTI can contribute to scarring, which may lead to hypertension and renal failure.

Most pediatric patients receiving chemotherapy receive pneumocystis jiroveci prophylaxis (exceptions may include those receiving targeted therapy or mildly cytotoxic therapy not causing lymphopenia). TMP-SMZ dosed on an intermittent schedule (3 days weekly) is most commonly used.[15] Whether the use of TMP-SMZ prevented UTIs in our patient population is speculative, because it did not reduce the rate of recurrent febrile UTIs after a first febrile UTI in children without cancer in children in the age range of 2 months to 7 years[16] or only modestly did so in children younger than 18 years.[17] We 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.

CONCLUSION

UTIs are as common in pediatric oncology patients with fever and neutropenia as they are in the non-neutropenic pediatric population. The diagnostic evaluation of a pediatric oncology patient with febrile neutropenia should include urinalysis and urine culture. Although the number of patients with UTI in our study was small, the use of TMP-SMZ prophylaxis may be beneficial in preventing UTI in this susceptible population.

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