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BRIEF REPORT

Utility of Urine Cultures During Febrile Neutropenia Workup in Hematopoietic Stem Cell Transplantation Recipients Without Urinary Symptoms

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The utility of obtaining screening urine cultures for febrile neutropenia (FN) during hematopoietic stem cell transplant (HCT) is unknown. In 667 adult HCT patients with FN, only 40 (6%) were found with bacteriuria. Antibiotics were modified in 3 patients (0.4%) based on urine cultures and none developed urinary-associated infectious complications.

Keywords. blood and marrow transplant; febrile neutropenia; hematopoietic stem cell transplantation; urinary tract infection; urine culture.

Hematopoietic cell transplantation (HCT) is a life-saving treatment for patients with hematologic malignancy [1]. Hematopoietic cell transplantation is associated with increased risk of severe infection, in part, due to prolonged neutropenia after conditioning chemotherapy and/or radiation [2]. Although the incidence of febrile neutropenia (FN) after HCT is estimated to be as high as 80%, only 20%–25% of FN episodes result from microbiologically documented infections [3]. Identification of urinary tract infections (UTIs) during FN may be complicated by the potential absence of pyuria, and transplant centers take a variety of different approaches in evaluating HCT patients with FN for UTIs based on conflicting society guidelines [4–6].

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Current data are limited to retrospective studies in adult patients with hematologic malignancies, which found that urine culture results rarely impacted antibiotic choice or clinical outcomes in patients without urinary symptoms, suggesting that urine cultures should be limited to symptomatic patients [7–9]. This is the first study to investigate the utility of obtaining urine cultures in HCT recipients with FN in a large, single-center cohort.

METHODS

Study Design and Setting

We conducted a single-center, retrospective study of adult patients admitted to the University of North Carolina Medical Center (UNCMC) from April 1, 2014 to January 1, 2021 for HCT (UNC Institutional Review Board [IRB] no. 21-0852; PIs, R.S. and T.M.A.). We included patients ≥18 years of age undergoing HCT with documented FN during the first admission and a urine culture collected during the initial FN episode. A standard definition for FN was used (absolute neutrophil count of $<0.5 \times 10^9$ cells/L or $<1 \times 10^9$ cells/L predicted to decrease to $<0.5 \times 10^9$ cells/L over 48 hours and a single oral temperature ≥100.4°F [≥38°C]). Urine cultures were considered positive (ie, bacteriuria) at a threshold of 1×10^4 colony-forming units (CFU)/mL. This is in line with available data, which suggests that a lower threshold than the widely accepted 1×10^5 CFU/mL should be considered in vulnerable groups, such as those with FN [10]. Urinary tract infections (UTIs) were defined by the presence of both urinary symptoms (dysuria, frequency, hematuria, acute incontinence, flank pain, or suprapubic pain) and bacteriuria of $\geq 10^4$ CFU/mL [11]. Patients were excluded if they had a documented UTI occurring within 7 days before admission for HCT. Asymptomatic bacteriuria is defined by the absence of urinary symptoms noted in the chart (dysuria, frequency, hematuria, acute incontinence, flank pain, or suprapubic pain) at the time the urine culture was obtained. Final clinical adjudication for asymptomatic bacteriuria was independently performed by R.S. and T.M.A.

Institutional protocol for FN workup in HCT recipients at UNCMC includes blood cultures, urinalysis, and urine culture, collected before antibiotic initiation. *Pneumocystis jirovecii* pneumonia prophylaxis (trimethoprim-sulfamethoxazole) is started at admission, held before cellular infusion (day 0), and is restarted at day of platelet recovery posttransplant. Antimicrobial prophylaxis with levofloxacin 500 mg, fluconazole 400 mg, and valacyclovir 500 mg are initiated on the day of transplant. Empiric antimicrobial therapy for FN includes cefepime, with escalation to broader spectrum antibiotics in those with compelling indications (eg, piperacillin-tazobactam

or meropenem ± vancomycin). Determination of antibiotic appropriateness was based on antibiotic susceptibility results or by clinical assessment with final adjudication by T.M.A. and R.S. if antibiotic susceptibility was not available (eg, presumed sensitivity of *Streptococcus* spp to vancomycin).

Data were obtained via electronic health records. The primary outcome was a composite of either antibiotic changes based on urine culture results or the development of severe urinary infectious complications including pyelonephritis, UTI-related bacteremia, or escalation to a higher level of care (eg, intensive care unit) due to UTI. Secondary outcomes included 30-day infectious-related mortality and 30-day all-cause mortality. Factors predisposing to asymptomatic bacteriuria, specifically diabetes and urinary tract abnormalities at the time of transplant, were compared for patients with asymptomatic bacteriuria and a matched cohort of patients without bacteriuria (matched for age, sex, and transplant type). Determination for whether antibiotics were modified as a result of clinicians' knowledge of urine cultures was made based on the timing of antibiotic changes relative to urine culture results and mention of these modifications in patients' notes. Final adjudication for antibiotic modification as a result of urine cultures was performed independently and then by consensus among R.S., T.M.A., and M.Tra.

Patient Consent Statement

The study design, including a waiver of patient consent, was approved by the UNC Institutional IRB, consistent with US standards.

Statistical Methods

Patient characteristics were summarized using descriptive statistics, primarily frequency tables. Fisher's exact test was used to compare percentages between groups for nominal categorical variables. The Wilcoxon 2-group test was used to compare continuous variable (eg, age). All reported *P* values are 2-sided, with *P* values less than .05 considered significant. Statistical analyses were performed using both SAS (version 9.4; SAS Institute, Cary, NC) and R (version 4.1.1, 2021; R Foundation for Statistical Computing, Vienna, Austria) [12, 13].

RESULTS

Baseline Characteristics

A total of 1136 HCT admissions for 1062 patients at the University of North Carolina between 2014 and 2021 were screened, and 667 patients were identified who met inclusion criteria (Supplementary Figure 1). Of the 667 patients, 40 (6%) were found to have bacteriuria at the time of FN without urinary symptoms (asymptomatic bacteriuria). The median age of patients was 58 (19–78) years and most were male (63%), undergoing autologous HCT (68%), primarily for multiple myeloma (41%). Table 1 illustrates baseline characteristics for patients with asymptomatic bacteriuria versus those without bacteriuria. There were no significant differences between those with asymptomatic bacteriuria versus nonbacteriuria except for a higher percentage of female patients in the former (68% vs 35%, $P = .0001$). None of the patients had urinary catheters at the time of urine culture. Underlying risk factors for

Table 1. Baseline Characteristics of Patients With Urine Cultures for Febrile Neutropenia Undergoing Hematopoietic Stem Cell Transplantation

		Asymptomatic Bacteriuria and Nonbacteriuria (n = 667)		
Variables	All (n = 667)	Asymptomatic Bacteriuria (n = 40)	Nonbacteriuria (n = 627)	*P* Value
Age at transplant, median (range)	58 (19–78)	60 (25–74)	58 (19–78)	.64
Female, n (%)	246 (37%)	27 (68%)	219 (35%)	< .0001
Transplant type, n (%)				
Autologous	455 (68%)	25 (63%)	430 (69%)	.48
Allogenic	212 (32%)	15 (37%)	197 (31%)	
Myeloablative	114 (54%)	6 (40%)	108 (55%)	.41
Cancer diagnosis, n (%)				
MM/AL/PCD	280 (42%)	19 (48%)	261 (42%)	.65
AML/ALL	124 (19%)	11 (28%)	113 (18%)	
CML/CLL/SLL	9 (1%)	0 (0%)	10 (1%)	
MDS/MPN/MPS/MF/AA	60 (9%)	3 (8%)	56 (9%)	
NHL	138 (20%)	5 (12%)	132 (21%)	
HL	38 (6%)	1 (2%)	37 (6%)	
Others*	18 (3%)	1 (2%)	18 (3%)	
Timing of antibiotics relative to urine culture, median days (range)	0 (–20 to +6)	0 (–10 to 0)	0 (–20 to +6)	.67
Total duration of antibiotics, median (range)	6 (0–102)	6 (2–50)	6 (0–102)	.76

Abbreviations: AA, aplastic anemia; AL, amyloidosis; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MF, myelofibrosis; MM, multiple myeloma; MPN, myeloproliferative neoplasm; MPS, myeloproliferative syndrome; NHL, non-Hodgkin lymphoma; PCD, plasma cell disorder; SLL, small lymphocytic lymphoma.

*Others: angioimmunoblastic T-cell lymphoma, germ cell tumor, hemophagocytic lymphohistiocytosis, sick cell anemia.

Table 2. Comparison of Urinalysis Results Between Patients With Symptomatic Nonbacteriuria, Asymptomatic Bacteriuria, and Nonbacteriuria

…	Total (n = 650)	Symptomatic Nonbacteriuria (n = 6)	Asymptomatic Bacteriuria (n = 40)	Asymptomatic Nonbacteriuria (n = 604*)	*P* Value
Any WBCs	488 (75%)	6 (100%)	27 (68%)	455 (75%)	.20
WBC, median (range)	1 (0–127)	2 (1–48)	1 (0–18)	1 (0–127)	.48
Leukocyte esterase	8 (1%)	0	0	8 (1%)	.99

Abbreviations: WBC, white blood cell.

*Includes only those patients with a urinalysis performed at the time of urine culture.

Table 3. Cultured Bacterial Strains Identified in Urine Cultures of Patients With Asymptomatic Bacteriuria

Bacterial Strains (n = 41)	n (%)
Gram-Negative Rods	
Escherichia coli	3 (7.3)
Citrobacter freundii	1 (2.4)
Enterobacter cloacae	1 (2.4)
Pseudomonas aeruginosa	1 (2.4)
Total	6 (14.5)
Gram-Positive Cocci	
CoNS	20 (48.8)
MRSA	3 (7.3)
Enterococcus faecalis	3 (7.3)
Enterococcus faecium	2 (4.9)
Streptococcus mitis	2 (4.9)
Total	30 (73.2)
Gram-Positive Rods	
Lactobacillus spp	3 (7.3)
Corynebacterium urealyticum	1 (2.4)
Diphtheroids[a]	1 (2.4)
Total	5 (12.1)

Abbreviations: CFU, colony-forming units; CoNS, coagulase-negative staphylococci; MRSA methicillin-resistant *Staphylococcus aureus*.

[a]Diphtheroids: *Corynebacterium* spp thought to be commensal bacteria of the skin and of uncertain pathogenicity in immunocompromised individuals.

bacteriuria, such as diabetes and urinary tract abnormalities at the time of transplant, were investigated between patients with asymptomatic bacteriuria (n = 40) and matched controls without bacteriuria (n = 40, see Methods); no differences were observed between groups (Supplementary Table 1).

All patients received prophylactic antibiotics at the time of transplant with levofloxacin being the most common antibacterial agent (92%) (Supplementary Table 2). All patients with FN received empiric IV antibiotics after transplant with the majority receiving cefepime (78%) (Supplementary Table 3). There were no significant differences in antimicrobial prophylaxis or empiric treatment observed between this group of patients and those without bacteriuria except for a slightly higher percentage of patients who received cefdinir in the asymptomatic bacteriuria group (10% vs 2%, $P = .04$ for all antibacterial prophylaxis). Patients with bacteriuria did not significantly differ from the nonbacteriuria group in timing of antibiotics relative to urine culture, total duration of antibiotics during hospitalization (Table 1), or urinalysis results (Table 2).

Urine Culture Results and Clinical Outcomes

In the 40 (6%) patients with asymptomatic bacteriuria, 41 bacterial strains were identified, with the most common being coagulase-negative *Staphylococcus* spp (CoNS), *Enterococcus* spp, *Staphylococcus aureus*, *Escherichia coli*, and *Lactobacillus* spp (Table 3). There were 7 patients (1%) with reported urinary symptoms, and only 1 with a positive urine culture who was excluded from further analysis (CoNS; other causes include BK cystitis n = 5 and chemotherapy toxicity n = 1). Antibiotic changes were made in only 3 patients based on urine culture results (0.4%) (Supplementary Table 4). No patients developed symptomatic UTI, pyelonephritis, or UTI-related bacteremia or required escalation of care due to infection from a urinary source. Of those with asymptomatic bacteriuria, no differences in time to resolution of fever, escalation of care, or duration of hospitalization were observed between those on "clinically appropriate antibiotics" (as defined under Methods) within 24 hours of urine culture (n = 23 or 58%) versus those not on appropriate antibiotics (Supplementary Table 5). One hundred twenty-eight patients of the 667 included (19%) had a positive blood culture during transplant admission, 6 of whom (0.9%) had the same pathogen identified in both blood and urine cultures (methicillin-resistant *S aureus*, *Staphylococcus epidermidis*, and *Enterobacter cloacae*) (Supplementary Table 6). No bacteremia episodes were believed to be from a urinary source. No patients in the asymptomatic bacteriuria group died within 30 days posttransplant, in comparison to 11 patients (0% vs 1.8%, $P = .64$) who died in the nonbacteriuria group. Mortality in this latter group was not attributable to any infectious complications.

DISCUSSION

Antimicrobial resistance is an increasing threat to the effective management of severely immunocompromised patients, particularly those undergoing HCT. Although antimicrobial stewardship has grown in priority among transplant centers, recognition of the importance of diagnostic stewardship has continued to lag. Limiting urine cultures to those patients

with FN who are symptomatic is one example of diagnostic stewardship that transplant centers across the country are increasingly embracing, although with little data to support their efforts. To the best of our knowledge, this is the only analysis to date assessing the utility of routine urine cultures in HCT patients with FN.

CONCLUSIONS

Our results provide preliminary evidence against the use of urine cultures in FN patients undergoing HCT without urinary symptoms. Although these findings are consistent with reports in patients with hematologic malignancies and may apply more broadly to those with FN outside of HCT, further studies are warranted. As rates of antimicrobial resistance rise, implementing antimicrobial stewardship together with diagnostic stewardship is likely to offer a more comprehensive and effective approach to preserving the utility of our most widely used broad-spectrum antimicrobials.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors: No reported conflicts of interest.

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