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Antimicrobial therapy for asymptomatic bacteriuria or candiduria in advanced cancer patients transitioning to comfort measures

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Abstract

Among 300 advanced cancer patients with potential urinary tract infection (UTI), 19 had symptomatic UTI. Among remaining patients (n = 281), 21% had asymptomatic bacteriuria or candiduria, and 14% received inappropriate therapy for 279 antimicrobial days. Bacteriuria or candiduria predicted antimicrobial therapy. At 10,000 to <100,000 CFU/mL, the incidence rate ratio [IRR] was 16.9 (95% confidence interval [CI], 6.0–47.2), and at ≥100,000 CFU/mL, the IRR was 27.9 (95% CI, 10.9–71.2).

More than 80% of advanced cancer patients are treated for infection during terminal hospitalization.¹ Among these infections, urinary tract infections (UTIs) predominate; reports suggest that 39%–42% involve potential UTI among advanced cancer patients receiving hospice care.^{2,3} Nevertheless, diagnosing UTI in this population is challenging. Specifically, the identification of asymptomatic bacteriuria is complicated by immunosuppression and nonspecific clinical features. This is important because advanced cancer patients with potential UTI often receive antimicrobial therapy,^{2,3} including inappropriate therapy for asymptomatic bacteriuria.

The implications of inappropriate antimicrobial therapy for asymptomatic bacteriuria are unique in advanced cancer patients and extend beyond antimicrobial overuse. Antimicrobial therapy in those receiving palliative care should be concordant with goals of care by promoting comfort and quality of life.⁴ However, antimicrobial therapy for asymptomatic

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bacteriuria conflicts with palliative goals of care if it provides no symptom relief and promotes adverse effects. Moreover, administering antimicrobials may cause pain and introduce additional infection risk.

Evidence suggests antimicrobial stewardship interventions may reduce urine culture ordering and inappropriate antimicrobial therapy for asymptomatic bacteriuria in catheterized patients.⁵ Less is known regarding the impact of stewardship interventions in noncatheterized advanced cancer patients. We sought to evaluate the association between asymptomatic bacteriuria or candiduria and antimicrobial use in advanced cancer patients transitioning to comfort measures to inform stewardship interventions.

Methods

We conducted a cohort study of patients aged ≥ 65 years with advanced cancer who were transitioned to comfort measures during admission to Yale-New Haven Hospital, a 1,541-bed tertiary care center in New Haven, Connecticut, between July 1, 2014, and November 31, 2016. Advanced cancer was defined as stage 3–4 solid tumors; stage 3–4 lymphomas; or acute, refractory, relapsed, or active liquid tumors requiring chemotherapy or targeted therapies. All advanced cancers were identified by *International Classification of Diseases, Tenth Revision* codes and were confirmed on medical record review. We subsequently identified the subset of patients with potential UTI, defined as the collection of ≥ 1 urine culture during admission. The Yale Human Investigation Committee approved this study.

For all advanced cancer patients with potential UTI, we collected demographics, hospitalization information, urine catheter placement dates, urine culture results, and clinical features. Urine cultures were categorized as (1) no growth; (2) bacteriuria or candiduria $10,000$ to $<100,000$ colony forming units per milliliter (CFU/mL); or (3) bacteriuria or candiduria $\geq 100,000$ CFU/mL. Cultures with growth of ≥ 2 organisms were analyzed. Cultures with no growth, mixed flora (≥ 3 organisms), or growth $<10,000$ CFU/mL were defined as no growth. UTI-associated clinical features included fever ($>38^{\circ}\text{C}$), suprapubic tenderness, costovertebral angle pain or tenderness, urgency, frequency, or dysuria. Additional clinical features evaluated alternate criteria for UTI and included leukocytosis ($>14,000$ leukocytes/ mm^3), worsening mental status, urinary incontinence, and gross hematuria.⁶ Asymptomatic bacteriuria or candiduria was defined as urine culture growth without any UTI-associated clinical features independent of additional clinical features.

We determined whether patients met 2017 National Healthcare Safety Network (NHSN) symptomatic UTI criteria, defined as urine culture growth of ≥ 2 organisms including ≥ 1 bacterium with $\geq 100,000$ CFU/mL plus ≥ 1 UTI-associated clinical feature within a 7-day infection window encompassing the 3 calendar days before and after urine culture collection.⁷ Among patients without NHSN-defined symptomatic UTI, we determined whether UTI-specific antimicrobial therapy was administered and the duration of therapy in antimicrobial days. UTI-specific antimicrobial therapy was defined as antimicrobials prescribed for potential UTI according to physician documentation and continued for ≥ 1 calendar day after speciation data were reported.

Characteristics were provided as proportions with the specified attribute. Among patients without NHSN-defined symptomatic UTI, we determined the proportion that received UTI-specific antimicrobial therapy. To evaluate factors associated with UTI-specific antimicrobial therapy among patients without NHSN-defined symptomatic UTI, we used a modified Poisson regression model with antimicrobial administration as a binary outcome and length-of-stay as an offset variable. Potential risk factors included gender, cancer type, urine culture growth (no growth; 10,000 to <100,000 CFU/mL; or ≥100,000 CFU/mL), and UTI-associated clinical features. Given the high death rate, we accounted for time at risk and used robust variance estimators to estimate the adjusted incidence rate ratio (IRR) for each factor. All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

We identified 300 advanced cancer patients with potential UTI who were transitioned to comfort measures. Median age was 74 years (range, 65–99), 162 (54.0%) were female, and 66 (22.0%) had liquid tumors (Table 1). Median length-of-stay was 9 days (range, 2–138), and 173 patients (57.7%) died during hospitalization.

Overall, 536 urine cultures were collected, and 76.9% (n = 412) had no growth. Among the remaining 124 cultures, the most common organisms were *Escherichia coli* (n = 25), *Candida albicans* (n=21), and *Klebsiella pneumoniae* (n = 14).

Among 300 patients with potential UTI, 19 had NHSN-defined symptomatic UTI. Among the 281 patients without NHSN-defined symptomatic UTI, 21% (n = 59) had asymptomatic bacteriuria or candiduria, and 14.2% (n = 40) received inappropriate UTI-specific antimicrobial therapy for 279 antimicrobial days. Of these 40 patients, 35 had bacteriuria or candiduria, and 35 lacked UTI-associated clinical features (Table 2). The most commonly prescribed antimicrobials included ciprofloxacin (n = 12), fluconazole (n = 8), and piperacillin/tazobactam (n = 4).

In a multivariable model, administration of UTI-specific antimicrobial therapy was associated with bacteriuria or candiduria. For 10,000 to <100,000 CFU/mL, the IRR was 16.9 (95% confidence interval [CI], 6.0–47.2); for ≥100,000 CFU/mL, the IRR was 27.9 (95% CI, 10.9–71.2). However, UTI-specific antimicrobial therapy was not associated with gender (IRR, 1.0; 95% CI, 0.6–1.8), cancer type (IRR, 0.7; 95% CI, 0.4–1.4), or UTI-associated clinical features (IRR, 1.3; 95% CI, 0.7–2.7).

Discussion

We show that most advanced cancer patients with potential UTI lack evidence of NHSN-defined symptomatic UTI. Moreover, 21% of patients without NHSN-defined symptomatic UTI had asymptomatic bacteriuria or candiduria. Patients without NHSN-defined symptomatic UTI were nevertheless treated for UTI, often with broad-spectrum antimicrobials associated with adverse effects,⁸ for 279 antimicrobial days after urine culture speciation data were reported. Such inappropriate antimicrobial therapy was independently associated with bacteriuria or candiduria rather than UTI-associated clinical features.

Collectively, this study highlights a potential target of antimicrobial stewardship, namely, restricting urine culture orders in advanced cancer patients transitioning to comfort measures.

Our work confirms published findings⁹ and supports guidelines recommending urine culture evaluation only in the presence of UTI-associated clinical features.¹⁰ Few studies have examined inappropriate urine cultures in end-of-life advanced cancer patients, a population in whom unnecessary antimicrobials may cause harm and conflict with comfort-oriented goals of care. We show that advanced cancer patients with bacteriuria or candiduria were 17–28 times more likely to receive UTI-specific antimicrobial therapy per patient day when compared to those without bacteriuria or candiduria. Our data further suggest that nonspecific additional clinical features such as leukocytosis may drive antimicrobial administration in those without UTI-associated clinical features. Future studies should evaluate the impact of urine culture order restrictions in end-of-life advanced cancer patients.

This study has limitations. First, the sample size precluded evaluation of other factors predisposing to antimicrobial therapy such as family preferences. However, the strength of the observed adjusted association suggests bacteriuria and candiduria will remain associated with UTI-specific antimicrobial therapy. Second, NHSN definitions may lack sensitivity for symptomatic UTI in older adults.⁶ However, of the 19 patients with additional clinical features in the setting of bacteriuria or candiduria and absent UTI-associated clinical features, none met revised McGeer criteria for UTI.⁶ Finally, our results may lack generalizability to other institutions.

In summary, many advanced cancer patients with potential UTI have asymptomatic bacteriuria or candiduria for which inappropriate antimicrobial therapy was administered for extended periods. Bacteriuria or candiduria was associated with UTI-specific antimicrobial therapy, suggesting that stewardship interventions should consider restricting urine cultures in this population.

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Table 1.

Characteristics of Hospitalized Advanced Cancer Patients With Potential Urinary Tract Infection Who Were Transitioned to Comfort Measures at a Tertiary-Care Medical Center (n = 300)

Characteristic	No. (%)
Age	
65–74 y	159 (53.0)
75–84 y	105 (35.0)
85 y	36 (12.0)
Gender	
Female	162 (54.0)
Male	138 (46.0)
Race	
White	227 (75.7)
Black	41 (13.7)
Other	32 (10.7)
Cancer type	
Nonliquid tumor ^a	234 (78.0)
Liquid tumor ^b	66 (22.0)
Selected comorbidities	
Cardiovascular ^c	52 (17.3)
Diabetes	56 (18.7)
Pulmonary disease	32 (10.7)
Code status on admission	
Full code	253 (84.3)
No resuscitation, no intubation, or both	45 (15.0)
Comfort measures ^d	2 (0.7)
Hospital interventions	
Intensive care unit admission	191 (63.7)
Vasopressor support	89 (29.7)
Mechanical ventilation	22 (7.3)
Tube feeding	78 (26.0)
Hemodialysis	4 (1.3)
Length of stay	
1 to <3 d	10 (3.3)
3 to <7 d	85 (28.3)
7 d	205 (68.3)

^aIncludes lung tumor, gastrointestinal tumor and other solid tumor including genitourinary cancer, breast cancer, female reproductive cancer, melanoma, head and neck cancer, connective tissue cancer, central nervous system cancer, thyroid, and unknown primary.

^bIncludes lymphoma, myeloid malignancy, plasma cell malignancy, and lymphoid malignancy.

^cIncludes myocardial infarction, congestive heart failure, and peripheral vascular disease.

^dThese 2 patients changed to a non-comfort-measures code status during admission and subsequently transitioned to comfort measures prior to discharge.

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Table 2.

Antimicrobial Use According to Urine Culture Results and Clinical Features in Hospitalized Advanced Cancer Patients Transitioned to Comfort Measures With Potential Urinary Tract Infection (UTI) who Lack National Healthcare Safety Network-Defined Symptomatic UTI

Urine Culture	UTI-Associated Clinical Features ^a (Total No. Patients)			Antimicrobial Use, Yes	Antimicrobial Use, No
Bacteriuria or Candiduria (≥ 100,000 CFU/mL)	Present (1)		1 ^b		0
Bacteriuria or Candiduria (≥ 100,000 CFU/mL)	Absent (29)		18 ^c		11
Bacteriuria or Candiduria (10,000 CFU/mL, <100,000 CFU/mL)	Present (5)		3		2
Bacteriuria or Candiduria (10,000 CFU/mL, <100,000 CFU/mL)	Absent (30)		13 ^d		17
No growth	Present (25)		1		24
No growth	Absent (191)		4		187

^aUTI-associated clinical features were defined as fever (>38°C), suprapubic tenderness, costovertebral angle pain or tenderness, urinary urgency, urinary frequency, or dysuria.

^bThis patient had candiduria alone and therefore did not meet National Healthcare Safety Network criteria for symptomatic urinary tract infection.

^cAdditional clinical features were present in 13 total patients, including 10 with leukocytosis (>14,000 leukocytes/mm³) and 7 with worsening mental status.

^dAdditional clinical features were present in 6 total patients, including 3 with leukocytosis (>14,000 leukocytes/mm³), 4 with worsening mental status, and 1 with urinary incontinence.